Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: May 15, 2009

FROM: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the June 16, 2009 AAC Meeting to Discuss BLA 125293 for pegloticase (Krystexxa) for the treatment of refractory gout

Pegloticase is a recombinant PEGylated (polyethylene glycol-ylated) form of the porcine uricase enzyme developed to lower serum uric acid and treat the signs and symptoms of gout in patients with gout refractory to conventional treatments. Patients with gout who have recurrent episodes of gouty arthritis or who develop tophi (deposits of uric acid in tissues) are treated with drugs to reduce uric acid levels. Some patients do not respond to, or are intolerant of, usual treatments for lowering uric acid. The clinical development program for pegloticase included studies of 8 mg/kg every 2 weeks and every 4 weeks. If approved, pegloticase would be the first uricase product marketed in the United States. Pegloticase is proposed for use at a dose of 8 mg/kg by intravenous infusion every 2 weeks.

The Applicant, Savient, Inc., has submitted data for efficacy of both the every 2 week and every 4 week dose regimens. The Agency does not dispute the efficacy of pegloticase at these doses. Rather, the Agency presentation will focus on safety issues identified during review of the application. During review of the two Phase 3 studies the Agency determined that there were safety issues of concern: 1) a greater proportion of patients treated with pegloticase than placebo-treated patients developed serious cardiovascular events; 2) a greater proportion of patients treated with pegloticase developed infusion reactions and allergic reactions and 3) the majority of patients receiving pegloticase

developed antibodies to pegloticase with adverse effects on safety and efficacy. Because most of the patients developing the serious cardiovascular adverse events had other cardiovascular risk factors and because of the small numbers of events in each study arm there was uncertainty concerning whether the cardiovascular adverse events represent a genuine safety signal or whether they represent expected adverse events related to underlying risk factors.

During this meeting, you will hear presentations from the Applicant, Savient Pharmaceuticals, and from the Agency, who will discuss:

- the clinical development program for pegloticase; and
- data from the clinical trials performed to assess the safety and efficacy of pegloticase.

Following these presentations, you will be asked to assess these findings and to discuss the risks and benefits of pegloticase in patients with treatment-refractory gout. We will ask the committee to address whether the evidence indicates that pegloticase increases cardiovascular risk and whether further studies are needed to evaluate that risk. We will ask the committee to discuss the clinical utility of pegloticase in the treatment of refractory chronic gout. We will ask the committee whether the Applicant has presented adequate data to determine whether the potential benefits of pegloticase outweigh the potential risks. We will ask the committee to discuss the appropriate patient population and appropriate frequency of monitoring of patients if pegloticase is approved. Finally, we will ask the committee what postmarketing studies would be appropriate if pegloticase is approved.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Briefing Document for the Arthritis Advisory Committee Meeting

June 16, 2009

Krystexxa™/Pegloticase BLA 125293

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products
Silver Spring, MD 20993

Table of Contents

Background

Gout is an ancient malady whose earliest clinical description has been attributed to Hippocrates in the 5th century BC. It is a metabolic syndrome frequently associated with hyperuricemia characterized by episodic attacks of inflammatory arthritis as a result of monosodium urate (MSU) crystal deposition in articular and periarticular tissue. Although gout is classified as a crystal-induced arthropathy, patients with this disease may also develop non-articular systemic manifestations such as tophi (discrete nodular aggregates of MSU in soft tissue), renal calculi and parenchyma disease due to the precipitation of uric acid in these areas.

Gout most commonly affects middle-aged men over age 40 and postmenopausal women with a male-to-female ratio of 4:1[1, 2]. Based on self-reported population data collected by the 1988-1994 Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of gout in the United States has been estimated to be approximately 2.7% and rises with increasing age to 9% in men and 6% in women over 80 years of age[2]. Epidemiologic studies indicate that the prevalence of this disease in both sexes has steadily been rising in this country[1, 3].

Factors that may help explain the increasing prevalence of gout include increasing rates of conditions associated with a higher risk of gout. These include obesity, hypertension, hyperlipidemia, the metabolic syndrome, organ transplantation, the use of diuretics (thiazides) and low dose salicylate, alcohol usage and purine-rich Western-style diets which can affect the body's balance between production and excretion of uric acid, thus producing elevated serum uric acid levels. In man, hyperuricemia results from the overproduction or the underexcretion of urate, or a combination of the two[2]. Urate that is produced by the body is excreted via the kidneys since humans do not produce the enzyme uricase. In contrast, animals handle uric acid both by excreting it via the kidneys and by metabolizing it into allantoin and hydrogen peroxide via uricase[2]. The ability to make uricase has been lost during evolution as evidenced by the fact that humans do not have a functional uricase gene.

Although the risk for gout increases directly with the level of hyperuricemia (defined as serum uric acid $\geq$ 7 mg/dL), not everyone with hyperuricemia will develop symptoms of this disease[4]. As uric acid levels increase above approximately 6-7 mg/dL the tendency of uric acid to precipitate out as urate crystals increases[2]. However, in addition to uric acid concentration a number of other factors influence the tendency of uric acid to precipitate out of solution including cation concentration, pH, temperature, and the presence of nucleating agents to promote the formation of urate crystals[2]. Precipitated MSU crystals are responsible for inciting the intense inflammatory response that is characteristic of an acute gout attack. In view of the established connection between hyperuricemia and gout, the goal for the management of gout is two-fold: 1) the treatment of acute attacks, and 2) the lowering of serum uric acid levels to prevent disease flares and associated sequelae such as gouty arthropathy, tophi and renal stones[5].

Standard of care for gout includes the use of nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine and ACTH for the treatment of acute attacks, and the use of either uricosurics (e.g., Probenecid) or xanthine oxidase inhibitors (e.g. allopurinol and febuxostat) to lower serum uric acid levels while ameliorating factors that contribute to hyperuricemia. The pharmacodynamic goal for urate lowering therapy is to reduce and maintain serum uric levels to less than the physiologic threshold for saturation of uric acid (i.e., < 6 mg/dL) to prevent continued deposition of crystals and clear the body of accumulated urate stores[5]. Tophi have been observed to resolve spontaneously. Data from several uncontrolled clinical trials with several urate lowering therapies have shown that lowering uric acid to below 6 mg/dL is associated with resorption of tophi[6, 7]. The rate of resorption of tophi is proportional to the level of urate achieved[7]. It may take years of chronic exposure to urate-lowering agents in order to achieve a reduction in the size of tophi[6,7]. In fact, complete resolution of tophi has never been demonstrated in a randomized controlled trial for any of the approved urate-lowering agents.

The above cited data establishing a connection between uric acid and gout provide the basis for the use of urate lowering as an endpoint for demonstrating the efficacy of new products for the treatment of chronic gout. In particular, the Agency has accepted an endpoint of lowering uric acid to 6 mg/dL or less for Phase 3 trials of new drugs for chronic gout.

The most commonly used urate-lowering drug is allopurinol[5]. However, its effectiveness is limited by a number of issues including the need to use lower doses in patients with renal insufficiency, failure to sufficiently lower serum uric acid levels due to subtherapeutic dosing, and an adverse event profile that includes gastrointestinal, hepatic, renal, hematological and skin toxicities that occur in an approximately 20% of patients who take this drug, as well as the occurrence of hypersensitivity reactions in 2-4% of patients that in some instances have been fatal. It is estimated that approximately 5% of patients are forced to discontinue allopurinol therapy due to the development of an adverse event. Febuxostat, which was recently approved earlier this year and does not require renal adjustment in dosing, may provide a therapeutic alternative for patients unable to tolerate allopurinol.

Pegloticase is a genetically engineered PEGylated recombinant porcine uricase (urate oxidase) that metabolizes uric acid into soluble allantoin for excretion by the kidney with hydrogen peroxide and carbon dioxide as oxidative byproducts. The Applicant, Savient Pharmaceuticals, proposes a dose of 8 mg every 2 weeks via intravenous infusion to control hyperuricemia and manage the signs and symptoms of treatment failure gout.

In addition to the evidence linking hyperuricemia to manifestations of gout there is also evidence that patients with hyperuricemia have a greater risk of cardiovascular disease[8,9]. Two hypotheses have been advanced to explain the association between hyperuricemia and cardiovascular risk. One is that patients with hyperuricemia often have other risk factors for cardiovascular disease. Indeed, hyperuricemia is often seen in association with features of the metabolic syndrome, which includes obesity, hypertension, type II diabetes mellitus, renal insufficiency and hyperlipidemia, all of which are associated with

an increased risk of cardiovascular disease[8]. The other hypothesis to explain the association between hyperuricemia and cardiovascular risk is that hyperuricemia by itself predisposes to cardiovascular risk[9]. The evidence supporting this second hypothesis comes, in part, from studies indicating that hyperuricemia is an independent risk factor for cardiovascular disease as well as from studies suggesting deleterious effects of high uric acid levels on blood pressure and on endothelial function[8,10].

Regulatory History

The Applicant developed pegloticase as a treatment for patients who were refractory to, or unable to tolerate, standard anti-hyperuricemic therapy. At that time, the mainstay of anti-hyperuricemic therapy for gout was allopurinol. Based on an estimated prevalence of approximately 100,000 patients with severe gout who have not responded, are allergic, or have some other contraindication to the use of standard antihyperuricemic therapy, and could benefit from treatment with pegloticase in view of its then projected risk benefit ratio (e.g., risk of oxidative damage and immunogenicity), the sponsor was granted orphan drug status on February 21, 2001, by the Agency's Office of Orphan Products Development. Subsequently, the Applicant conducted a Phase 1 study to evaluate the safety, tolerability and efficacy of pegloticase in lowering serum uric acid in patients with gout when administered via subcutaneous injections. This study was terminated early after a number of study participants developed urticarial reactions following study injections. After the results from a second preclinical repeat dose intravenous study in dogs failed to identify any potential immunological safety signals with intravenous administration, Phase 1 testing in humans resumed.

To reduce the likelihood of developing allergic reactions the Applicant subsequently investigated pegloticase by intravenous (IV) administration. A Phase 2 study of IV pegloticase was not limited by urticaria. However, there was a 44% incidence of infusion reactions. In addition, some patients developed gout flares upon treatment with pegloticase. At an end-of-Phase 2 meeting held on August 16, 2005, the agency told the Applicant that it would be important for them to develop a standard regimen to minimize the frequency and severity of gout flares and a standard regimen of prophylaxis for infusion reactions.

On October 31, 2008, the Applicant submitted a biological licensing application for pegloticase for patients with treatment refractory gout. The safety database was smaller than would ordinarily be expected for a product intended for chronic use because the patient population represents an orphan indication. The application was granted priority review and an advisory committed meeting was scheduled. On February 4, 2009, the Applicant submitted a major amendment consisting of additional analyses to address cardiovascular adverse events among pegloticase-treated patients. Consequently, the agency extended the review clock by 3 months and delayed the advisory committee meeting to permit review of the new information.

Of note, while the pegloticase application was under review, the Agency approved a new uric acid-lowering drug on February 13, 2009, febuxostat, that was shown to be superior to allopurinol at lowering uric acid to below the target level of 6 mg/dL.

Product Clinical Development

As part of their clinical development program for pegloticase for the control of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective, the sponsor conducted a total of six clinical studies: two Phase 1 trials (401 and 402), one Phase 2 trial (403), and three Phase 3 trials (405, 406 and 407). An additional Phase 3 trial (409) was initiated just prior to submission of this application. These studies are summarized in the following table:

Table 1- Key Design Features of Pegloticase Trials

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administ.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1					
Protocol C0401 Objectives: 1. Determine the single dose PK profile and safety of 5 ascending dose levels of pegloticase via SC injection 2. Determine the antibody response to the product 3, Evaluate the dose effect on plasma uric acid levels	Single-center, open-label, dose-escalating tolerance , safety and PK	Single dose of pegloticase 4 mg, 8 mg, 12 mg, and 24 mg via subcutaneous injection	**N=13** 4 Subjects per first 3 dose cohorts; 1 Subject in 24 mg cohort	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 7mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis despite conventional urate-lowering therapy	N/A
Protocol C0402 Objectives: 1. Determine single dose PK profile and safety 6 ascending doses of IV pegloticase 2. Assess the dose effect on plasma uric acid levels 3. Determine the products safety and immune response profiles	Single-center, open-label, dose-escalating tolerance , safety and PK	Single dose of pegloticase 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg and 12 mg via intravenous infusion	**N=24** 4 Subjects per dose cohort	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 7 mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis despite conventional urate-lowering therapy	N/A
Phase 2					
Protocol C0403 Objectives: 1. Assess the effect of multiple doses of pegloticase on SUA 2. Determine the multiple dose PK profile of pegloticase 3. Assess the safety and tolerability of multiple doses of pegloticase	Multicenter, randomized, open-label, parallel-group, dose-ranging, efficacy, safety, and PK	Pegloticase 4 mg q 2 wks, 8 mg q 2 wks, 8 mg q 4 weeks, 12 mg q 4 weeks for 3 months via intravenous infusion	**N=41** 4mg q 2 wks: 4/7 completed, 8mg q 2 wks: 8/ 8 completed; 8mg q 4 wks: 8/13 completed; 12 mg q 4 wks: 6/13 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: ≥ 1 tophus, and/or having experienced a gout flare within the previous 6 months and/or having chronic gouty arthritis for whom conventional urate-lowering therapy is contraindicated or has been ineffective	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during the treatment period
Phase 3					
Protocol C0405 Objectives: 1. Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations < 6mg/dL for at least 80% of the time during months 3 and 6 2. Reduction in tophus burden, frequency of gout flares, number of swollen and tender joints and improvement in patient reported outcomes	Multicenter, randomized, double-blind, placebo-controlled, 26-week, comparative parallel group study. Study utilized randomization ratio of 2:2:1 stratified by the presence or absence of tophi. 26 sites in U.S. and Mexico	Pegloticase 8 mg q 2 weeks and 8 mg q 4 weeks via intravenous infusion Placebo via intravenous infusion	**N= 104** **Pegloticase Groups:** q 2 weeks: 46 enrolled; 29 completed q 4 weeks: 46 enrolled; 32 completed **Placebo Group:** 24 enrolled; 20 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: 3 disease flares within 18 months, or ≥ gouty tophus, or gout arthritis; and history of hypersensitivity or failure to normalize PUA following ≥ 3 months treatment with allopurinol at maximum labeled dose (800 mg daily) or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting co-morbidity (e.g., renal impairment)	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6.

* Study C0401: Terminated.
Adapted from Sponsor's 5.2 Tabular Listing of All Clinical Studies located in Module 5

Table 1- Key Design Features of Pegloticase Trials (cont.)

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administ.	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 3 (cont.)					
Protocol C0406 **Objectives:** 1. Demonstrate superiority in response rate vs. placebo in percentage achieving plasma uric acid concentrations < 6mg/dL for at least 80% of the time during months 3 and 6 2. Reduction in tophus burden, frequency of gout flares, number of swollen and tender joints and improvement in patient reported outcomes	Multicenter, randomized, double-blind, placebo-controlled, 26-week, comparative parallel group study. Study utilized randomization ratio of 2:2:1 stratified by the presence or absence of tophi. Sites in United States and Mexico	Pegloticase 8 mg every 2 weeks and 8 mg every 4 weeks via intravenous infusion Placebo via intravenous infusion	**N=108** **Pegloticase Groups:** q 2 weeks: 44 enrolled; 30 completed q 4 weeks: 43 enrolled; 27 completed **Placebo Group:** 20 enrolled; 19 completed	Adults age ≥ 18 years with hyperuricemia defined as a PUA ≥ 8 mg/dL; a diagnosis of symptomatic gout defined as: 3 disease flares within 18 months, or ≥ gouty tophus, or gout arthritis; and history of hypersensitivity or failure to normalize PUA following ≥ 3 months treatment with allopurinol at maximum labeled dose (800 mg OD) or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting co-morbidity (e.g., renal impairment)	Proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6.
Open-Label Extension Studies					
Protocol C0407** **Objective:** Evaluate the long-term safety, treatment effect and durability of response	Multicenter, uncontrolled, open-label, 24-month continuation study in subjects who completed Protocol C0405 or C0406	Pegloticase 8 mg every 2 weeks and 8 mg every 4 weeks via intravenous infusion Observational group (no treatment)	**N=151** 149 subjects continuing Pegloticase 2 subjects in observational group	Subjects with gout who had completed Protocol 405 or 406	N/A
Protocol C0409 **Objective:** Evaluate the safety and clinical effect of re-exposure to a 24-week course of treatment in subjects whose last exposure to pegloticase has been > 1 year to study entry	Multicenter, uncontrolled, open-label, 24 week re-exposure study	Pegloticase 8 mg every 2 weeks via intravenous infusion	Target: 18 subjects Enrolled: 7	Subjects previously treated with intravenous pegloticase during Phase 1 and 2 studies (C0402, C0403, C0405, C0406, and C0407) whose last exposure to the product was > 1 year prior to study entry	N/A

**Studies C0407 and C0409: Ongoing.
Adapted from Sponsor's 5.2 Tabular Listing of All Clinical Studies located in Module 5

Design of Pivotal Studies C0405 and C0406

Pegloticase's efficacy as a urate-lowering agent was evaluated by the Applicant in two Phase 3 clinical efficacy trials, Studies C0405 and C0406, which utilized an identical study design. These trials were multicenter, double-blind, placebo-controlled, parallel group studies in patients with symptomatic gout and hyperuricemia who are unable to tolerate or failed to respond to conventional urate lowering agents (see Table 1 and

appendix for more details of inclusion/exclusion criteria). Potential study candidates with unstable angina, uncontrolled arrhythmia, non-compensated congestive heart failure, uncontrolled hypertension, end-stage renal disease or post-organ transplant were prohibited from participating in these trials. The common protocol for these studies mandated that all patients undergo a 1-week washout of all antihyperuricemic therapy prior to the administration of study product in addition to foregoing the use of these agents while participating in these trials. In anticipation of intercritical gout flares as a result of study treatment, all patients were also required to be taking prophylactic gout therapy comprised of either colchicine or a non-steroidal anti-inflammatory drug (NSAID) unless medically contraindicated for the duration of their study participation. Subjects were randomized in a 2:2:1 ratio stratified by the presence or absence of tophi to the following 3 treatment groups:

- Pegloticase 8 mg every 2 weeks via IV infusion
- Pegloticase 8 mg every 4 weeks via IV infusion
- Placebo infusion

Patients randomized to the pegloticase 8 mg every 4 weeks group were administered placebo infusions on alternating treatments to maintain study blind. To limit the occurrence of hypersensitivity and infusion reactions related to the product's immunogenicity observed during the Phase 1 and 2 studies, all patients received a standardized pre-treatment prophylaxis regimen consisting of 60 mg fexofenadine the night before each study infusion, followed by 60 mg dose of fexofenadine and 1000 mg acetaminophen the morning of the infusion, and 200 mg of hydrocortisone IV immediately prior to each infusion. Subjects who completed the study had an option of continuing treatment by enrolling into a 12-month open-label extension (Study 407).

The primary endpoint for these studies was the proportion of subjects maintaining a PUA concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6. Secondary endpoints included reduction of tophus burden, frequency of gout flares, number of swollen joints and tender joints, and a variety of quality of life parameters assessed via the SF-36 and HAQ-DI. The statistical analysis plan specified that while the primary endpoints for each of the Phase 3 trials were to be analyzed separately the secondary endpoints were to be analyzed based on pooled data from the two trials.

Patient Population Characteristics

As summarized in the following tables (Tables 2 and 3), the three treatment groups in the Phase 3 trials were generally well balanced with respect to baseline demographics and gout disease characteristics and history. The subjects who participated in these studies were overwhelmingly Caucasian males and had a mean age of 55 years. These patients were also overweight as evidenced by body mass index (BMI) of 33, which is consistent with the fact that obesity is a risk factor for gout. The majority (62%) of subjects reported that they did not drink alcohol, another risk factor for gout.

Table 2 – Demographic Characteristics of Subjects Enrolled in Combined Phase 3 Studies 405 and 406

	Pegloticase 8 mg q 2 weeks (N=85)	Pegloticase 8 mg q 4 weeks (N=84)	Placebo (N=43)	Total (N=212)
Age				
Mean (SD)	56 (16)	55 (13)	55 (12)	55 (14)
Gender				
Male	68 (80%)	69 (82%)	36 (84%)	173 (82%)
Female	17 (20%)	15 (18%)	7 (16%)	39 (18%)
Race:				
American Indian/Alaskan Native	3 (4%)	2 (2%)	1 (2%)	6 (3%)
Asian	2 (2%)	1 (1%)	0 (0%)	3 (1%)
Hispanic/Latino	13 (15%)	8 (10%)	3 (7%)	24 (11%)
Black	8 (9%)	12 (14%)	7 (16%)	27 (13%)
Pacific Islander/Native Hawaiian	3 (4%)	1 (1%)	1 (2%)	5 (2%)
White	54 (64%)	59 (70%)	30 (70%)	143 (68%)
Other	2 (2%)	1 (1%)	1 (2%)	4 2%)
Weight (kg)				
Mean (SD)	98 (22)	101 (28)	100 (27)	100 (26)
Height (cm)				
Mean (SD)	173 (10)	175 (11)	176 (11)	174 (11)
BMI (kg/m^2)				
Mean (SD)	33 (7)	33 (8)	32 (7)	33 (8)
Alcohol Consumption:				
Yes	33 (39%)	32 (38%)	15 (35%)	80 (38%)
No	52 (61%)	52 (62%)	28 (65%)	132 (62%)

Sponsor's Table 12; p. 49 of ISE

The overall mean duration of disease since the first gout attack was 17 years and the overall mean duration since the first diagnosis of gout was 15 years for the study population. A total of 57% of the subjects had crystal-proven disease. The mean number of gout flares over the last 18 months reported by the three treatment groups was similar (11 attacks per year). The majority of subjects (69%) described their gout flares as multiarticular (e.g., $\geq$ 2-3 joints) and moderate to severe (95%) in nature. Overall, 58% of the total study population had chronic synovitis and/or arthropathy due to gout and 73% had tophaceous deposits at baseline. A minority of patients (17%) reported a history of gout-related kidney disease with a mean number of renal colic episodes of 0.4 per year. Ninety-five percent of the subjects did not have another arthritis condition that could potentially interfere with study evaluations. Based on these data, the study population that participated in this trial had moderate to severe gout.

Table 3 – Summary of Subjects' Gout History and Disease Status (Intent-to-Treat [ITT] Population) Who Participated in Combined Phase 3 Studies 405 and 406

	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Number of Years Since First Gout Attack:				
Mean (SD)	**17 (12)**	**17 (10)**	**15 (10)**	**17 (11)**
Number of Years Since First Diagnosis of Gout:				
Mean (SD)	**15 (12)**	**16 (10)**	**13 (10)**	**15 (11)**
Confirmed Presence of Uric Acid Crystals:				
Yes	**48 (57%)**	**45 (54%)**	**27 (63%)**	**120 (57%)**
No	**37 (44%)**	**39 (46%)**	**16 (37%)**	**92 (43%)**
Number of Acute Flares in the Past 18 Months:				
Mean (SD)	**10 (11)**	**10 (11)**	**10 (16)**	**10 (12)**
Pattern of Acute Flares:				
Monoarticular (One Joint)	**28 (33%)**	**24 (29%)**	**12 (29%)**	**64 (31%)**
Oligoarticular (2-3 Joints)	**21(25%)**	**24 (29%)**	**19 (46%)**	**64 (31%)**
Polyarticular (> 3 Joints)	**35 (42%)**	**34 (42%)**	**10 (24%)**	**79 (38%)**
Severity of Acute Flares:				
Mild (Uncomfortable)	**7 (8%)**	**1 (2%)**	**3 (7%)**	**11 (5%)**
Moderate (Limiting)	**24 (29%)**	**27 (33%)**	**15 (37%)**	**66 (32%)**
Severe (Crippling)	**53 (63%)**	**54 (66%)**	**23 (56%)**	**130 (63%)**
Chronic Synovitis/Arthropathy:				
Yes	**50 (59%)**	**47 (56%)**	**26 (61%)**	**123 (58%)**
No	**35 (41%)**	**37 (44%)**	**17 (40%)**	**89 (42%)**
History of Gout-Related Kidney Disease:				
Yes	**12 (14%)**	**16 (19%)**	**7 (16%)**	**35 (17%)**
No	**73 (86%)**	**68 (81%)**	**36 (84%)**	**177 (84%)**
Tophi:				
Yes	**62 (73%)**	**64 (76%)**	**29 (67%)**	**155 (73%)**
No	**23 (27%)**	**20 (24%)**	**14 (33%)**	**57 (27%)**
Surgery for Gout (Excluding Arthrocentesis)				
Yes	**13 (15%)**	**20 (24%)**	**13 (30%)**	**24 (22%)**
No	**72 (85%)**	**64 (76%)**	**30 (70%)**	**84 (78%)**
Another Arthritis Condition Potentially Confounding Diagnosis of Gout:				
Yes	**5 (6%)**	**4 (5%)**	**2 (5%)**	**11 (5%)**
No	**80 (94%)**	**80 (95%)**	**41 (95%)**	**201 (95%)**
Number of Episodes of Renal Colic in the Past Year:				
Mean (SD)	**0.4 (1.9)**	**0.4 (2.7)**	**0.4 (1.6)**	**0.4 (2.2)**

Adapted Sponsor's Table 14; p.52 of ISE

Since these studies' protocols specifically targeted hyperuricemic gout patients with documented unresponsiveness and/or hypersensitivity to allopurinol, a summary of patient eligibility based on prior allopurinol exposure is shown in Table 4 below. Overall, 58% of patients reported that they could not use allopurinol either due to a history of allergy or hypersensitivity, or unresponsiveness to drug therapy.

Table 4 – Patient Eligibility as Per Allopurinol Treatment History for Enrollment in Phase 3 Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg q 2 weeks (N=85)	Pegloticase 8 mg q 4 weeks (N=84)	Placebo (N=43)	Total (N=212)
Allopurinol Ineffective	**16 (19%)**	**17 (20%)**	**5 (12%)**	**38 (18%)**
History of Allergy/Hypersensitivity	**40 (47%)**	**28 (33%)**	**17 (40%)**	**85 (40%)**
Renal Insufficiency	**12 (14%)**	**11 (13%)**	**10 (23%)**	**33 (16%)**
GI Intolerance	**12 (14%)**	**19 (23%)**	**6 (14%)**	**37 (17%)**
Other	**5 (6%)**	**9 (11%)**	**5 (12%)**	**19 (9%)**

Adapted Sponsor's Table 7; p. 50 Clinical Study 405 Report and Table 7; p. 51 Clinical Study 406 Report

The following table (Table 5) summarizes the co-morbid medical conditions reported by 10% or more of the subjects who participated in the Phase 3 trials**.** Overall, large percentages of the subjects in these studies suffered from a variety of diseases commonly associated with gout such as hypertension (71%), renal failure (30% for the combined terms renal failure and chronic renal failure), diabetes mellitus (22% for the combined terms insulin or non-insulin dependent) and obesity (17%).

Table 5 – Tabular Summary of Comorbid Medical Conditions Reported by > 10% of Subjects Who Participated in Studies 405 and 406 via MedDRA Body System (ITT Population)

MedDRA Body System Preferred Term	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Vascular Disorders:	**61 (72%)**	**60 (71%)**	**32 (74%)**	**153 (73%)**
Hypertension	61 (72%)	60 (71%)	30 (70%)	151 (71%)
Metabolism and Nutrition Disorders:	**53 (62%)**	**55 (65%)**	**24 (56%)**	**132 (62%)**
Hypercholesterolemia	21 (25%)	16 (19%)	7 (16%)	44 (21%)
Hyperlipidemia	15 (18%)	17 (20%)	9 (21%)	41 (19%)
Obesity	14 (16%)	14 (17%)	7 (16%)	35 (17%)
Diabetes Mellitus	11 (13%)	9 (11%)	7 (16%)	27 (13%)
Diabetes Mellitus Non-Insulin Dependent	12 (14%)	7 (8%)	1 (2%)	20 (9%)
Musculoskel. and Connective Tissue Dis.:	**51 (60%)**	**45 (54%)**	**25 (58%)**	**121 (57%)**
Immune System Disorders:	**45 (53%)**	**41 (49%)**	**23 (653%)**	**109 (51%)**
Drug Hypersensitivity	41 (48%)	32 (38%)	18 (42%)	91 (43%)
Gastrointestinal Disorders:	**42 (49%)**	**39 (46%)**	**18 (42%)**	**99 (47%)**
Renal and Urinary Disorders:	**36 (42%)**	**37 (44%)**	**18 (42%)**	**91 (43%)**
Renal Failure	19 (22%)	11 (13%)	5 (12%)	35 (17%)
Renal Failure Chronic	7 (8%)	14 (17%)	7 (16%)	28 (13%)
Nephrolithiasis	8 (9%)	6 (7%)	4 (9%)	18 (8%)
Glomerulonephritis	0 (0%)	2 (2%)	1 (2%)	3 (1%)
Cardiac Disorders:	**28 (33%)**	**23 (27%)**	**14 (33%)**	**65 (31%)**
Coronary Artery Disease	8 (9%)	9 (11%)	6 (14%)	23 (11%)
Atrial Fibrillation	9 (11%)	3 (4%)	4 (9%)	16 (8%)
Cardiac Failure Congestive	5 (6%)	5 (6%)	3 (7%)	13 (6%)
Cardiomyopathy	3 (2%)	4 (5%)	2 (5%)	9 (4%)
Bundle Branch Block Right	4 (5%)	0 (0%)	2 (5%)	6 (3%)
Angina Pectoris	1 (2%)	4 (5%)	0 (0%)	5 (2%)
Arrhythmia	4 (5%)	1 (1%)	0 (0%)	5 (2%)
Arteriosclerosis Coronary Artery	1 (2%)	1 (2%)	0 (0%)	2 (2%)
Nervous System Disorders:	**24 (28%)**	**26 (31%)**	**13 (30%)**	**63 (30%)**
Respirat., Thoracic and Mediastinal Dis.:	**21 (25%)**	**27 (32%)**	**15 (35%)**	**63 (30%)**
Psychiatric Disorders:	**19 (22%)**	**24 (29%)**	**14 (33%)**	**57 (27%)**
Investigations:	**22 (26%)**	**19 (23%)**	**10 (23%)**	**51 (24%)**
Gen. Disorders and Administ. Site Cond.:	**25 (29%)**	**12 (14%)**	**10(23%)**	**47 (22%)**
Skin and Subcutaneous Tissue Disorders:	**19 (22%)**	**15 (18%)**	**11 (26%)**	**43 (20%)**
Endocrine Disorders:	**15 (18%)**	**12 (14%)**	**4 (9%)**	**31 (15%)**
Infections and Infestations:	**11 (26%)**	**6 (15%)**	**1 (5%)**	**18 (17%)**
Blood and Lymphatic System Disorders:	**13 (15%)**	**8 (10%)**	**7 (16%)**	**28 (13%)**
Eye Disorders:	**11 (13%)**	**13 (15%)**	**3 (7%)**	**27 (13%)**

Adapted Sponsor's Table A6.1; p. 275-296 of IES.

Table 6 summarizes all of the cardiovascular-related conditions reported by subjects in Studies 405 and 406. The majority of patients (84%) who participated in these studies also had pre-existing cardiovascular disease including coronary artery disease (18%), cardiac arrhythmias (16%), and cardiac failure/left ventricular dysfunction (12%).

Table 6 – Tabular Summary of Number (%) of Patient Reported Cardiovascular-Related Conditions in Subjects Who Participated in Studies 405 and 406

Medical Condition	Pegloticase 8 mg q 2 wks (N=85)	Pegloticase 8 mg q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
At least one of the following cardiovascular conditions:	73 (86%)	71 (85%)	35 (81%)	179 (84%)
Cardiac Arrhythmias	19 (22%)	8 (10%)	7 (16%)	34 (16%)
Cardiac Failure/LV Dysfunction	12 (14%)	8 (10%)	6 (14%)	26 (12%)
Cerebrovascular Disease	4 (5%)	3 (4%)	1 (2%)	8 (4%)
Coronary Disease	14 (17%)	16 (19%)	9 (21%)	39 (18%)
Diabetes	24 (28%)	18 (21%)	8 (19%)	50 (24%)
Dyslipidemia	42 (49%)	41 949%)	20 (47%)	103 (49%)
Hypertension	62 (73%)	60 (71%)	31 (72%)	153 (72%)
Vascular Disease, Peripheral	7 (8%)	6 (7%)	3 (7%)	16 (8%)
Venous Thromboembolic Disease	3 (4%)	2 (2%)	2 (5%)	7 (4%)
Obesity (BMI ≥ 30)	50 (59%)	55 (66%)	24 (56%)	129 (61%)
Chronic Kidney Disease	26 (31%)	25 (30%)	9 (21%)	60 (28%)
Sleep Apnea	8 (9%)	9 (11%)	6 (14%)	23 (11%)

LV = Left ventricular; BMI = body mass index
Adapted Sponsor's Table 20; p. 58 of updated ISS

Subjects' Disposition

A tabular summary of subjects' disposition from the pooled pivotal studies is shown in Table 7:

Table 7 – Subject Disposition for Combined Studies 405 and 406

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)	Total (N=212)
Number of Patients Randomized	90	89	46	225
Number of Patients Treated (ITT)	85	84	43	212
Number of Patients with Evaluable Tophi	62	64	29	155
Number of Patients that Completed Study 405 or 406:	**59 (69%)**	**59 (70%)**	**39 (91%)**	**157 (74%)**
Continued on OLE	57 (97%)	56 (95%)	38 (97%)	151 (96%)
Did Not Continue on OLE	2 (3%)	3 (5%)	1 (3%)	6 (4%)
Number of Patients Withdrawn Prematurely Before Week 24 from Study 405 or 406:	**26 (31%)**	**25 (30%)**	**4 (9%)**	**55 (26%)**
Non-compliance	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
Adverse Event[1]	16 (19%)	17 (20%)	1 (2%)	34 (16%)
Withdrew Consent	7 (8%)	6 (7%)	1 (2%)	14 (7%)
Lost to Follow-Up	0 (0%)	0 (0%)	2 (5%)	2 (1%)
Protocol Violation	1 (1%)	0 (0%)	0 (0%)	1 (0.5%)
Death	2 (2%)	1 (1%)	0 (0%)	3 (1%)

OLE = Open Label Extension; ITT = Intent to Treat Population
[1]Note: Based on review of patient narratives this includes the final disposition of Subject 308-003 pegloticase q 2 weeks and Subject 319-004 pegloticase q 4 weeks who discontinued treatment due to infusion reaction adverse events instead of withdrawal of consent and lost to follow up.
Adapted Sponsor's Table 11; p. 48 from ISE

A total of 225 patients were randomized in the combined studies, out of which 212 (94%) were considered the intent to treat (ITT) population on which all the primary and secondary efficacy analyses were conducted. A total of 115 (73%) patients had evaluable tophi. The overall rate of study completion was 74% with more placebo-treated patients (91%) completing the study as compared to patients randomized to the pegloticase every 2 weeks (69%) and every 4 weeks (70%) treatment groups. A majority (96%) of the patients who completed the studies went on to participate in the open-label extension (Study 407). The major reasons for discontinuation were similar for the two pegloticase treatment groups, but differed from that of the placebo group. The most common reason for early study withdrawal was adverse events in both the pegloticase every 2 weeks (19%) and pegloticase every 4 weeks (20%) treatment groups, which was nearly nine times the rate seen in the placebo group (2%). More patients also withdrew earlier from the study due to withdrawal of consent in the pegloticase every 2 weeks group (8%) and pegloticase every 4 week group (7%) as compared to the placebo group (2%). The major reason for early withdrawal for placebo-treated patients was lost to follow-up (5%) as compared to no patients withdrawing for this reason from the pegloticase treatment groups. Note that the subjects who withdrew from the study before month 6 were, by protocol definition, considered nonresponders for the primary efficacy analysis in the ITT group. Among patients who received at least one dose of study medication there were no deaths in the placebo population, but a total of 3 deaths occurred in patients treated with pegloticase (2 subjects in the every 2 weeks group and 1 subject in the every 4 weeks

group). One death occurred in a patient randomized to placebo; however, this patient died before receiving study medication. Receiving at least one dose of study medication was required, by protocol definition, for inclusion in the ITT group and thus this placebo patient was not included in the ITT analyses.

Efficacy

Primary Efficacy Endpoint

The primary endpoint for both of the Phase 3 trials was the proportion of subjects who maintained a plasma uric acid (PUA) concentration < 6 mg/dL for at least 80% of the time during Months 3 and 6 versus placebo. For statistical purposes, patients who were able to normalize their PUA to < 6 mg/dL and maintained it for at least 80% of the time during Months 3 and 6 were classified as "responders." For the primary analyses, patients who withdrew from the study before Month 6 were imputed as non-responders. Intermittent missing pre-dose PUA values were imputed with the baseline PUA level for that subject. Other intermittent missing PUA values were replaced by the average of the scores at the immediately previous and the next available time points for that subject.

Table 8 – Primary Efficacy Endpoint: PUA < 6mg/dL for at Least 80% of the Time in Months 3 and 6 Combined For Studies 405 and 406 (ITT Population)

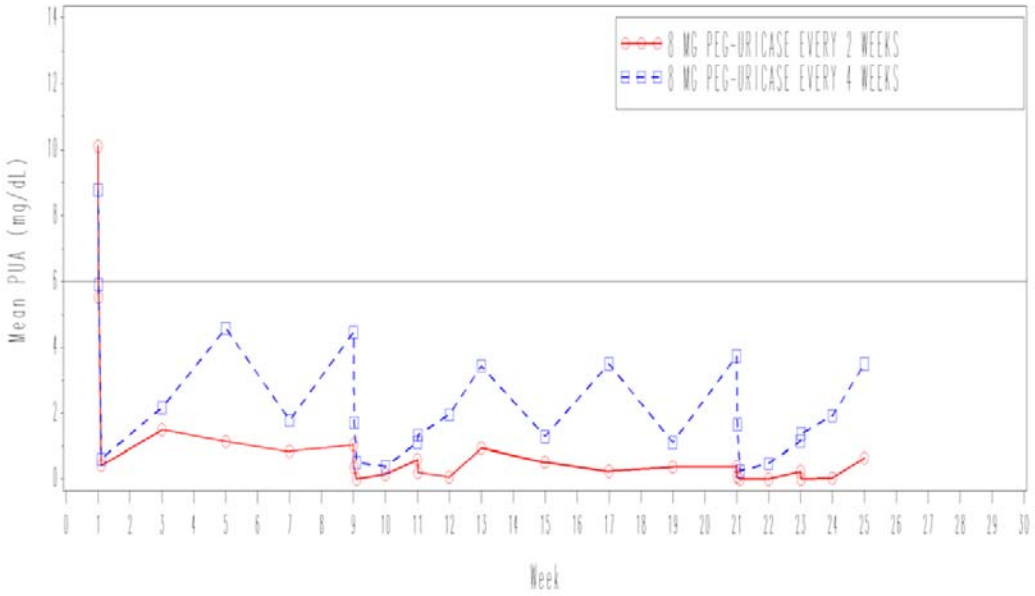
Treatment Group	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval[1]	P-Value[2]
Study 405			
Pegloticase q 2 Wks (N= 43)	**20 (47%)**	**[32%, 61%]**	**p<0.001**
Pegloticase q 4 Wks (N=41)	**8 (20%)**	**[7%, 32%]**	**p=0.044**
Placebo (N=20)	**0 (0%)**		
Study 406			
Pegloticase q 2 Wks (N=42)	**16 (38%)**	**[23%, 53%]**	**p<0.001**
Pegloticase q 4 Wks (N=43)	**21 (49%)**	**[34%, 64%]**	**p<0.001**
Placebo (N=23)	**0 (0%)**		

[1]95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo
[2]P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.
Adapted Sponsor's Table 11; p. 58 and Table 11; p. 57 from the clinical reports for Studies 405 and 406, respectively.

As shown in Table 8, for both studies, a greater proportion of patients achieved the primary endpoint in both the pegloticase every 2 weeks (47% and 38% in studies 405 and 406, respectively) and every 4 weeks (20% and 49% in Studies 405 and 406, respectively) treatment groups as compared to placebo (0% and 0% in each study). The differences between each of the treatment groups and the placebo groups were statistically significant in both Study 405 ($p < 0.001$ for pegloticase every 2 weeks versus placebo and $p = 0.044$ for pegloticase every 4 weeks versus placebo) and Study 406 ($p < 0.001$ for each pegloticase treatment group versus placebo). Figures 1 and 2 below, graphically depict the mean PUA concentration profile for responders and non-

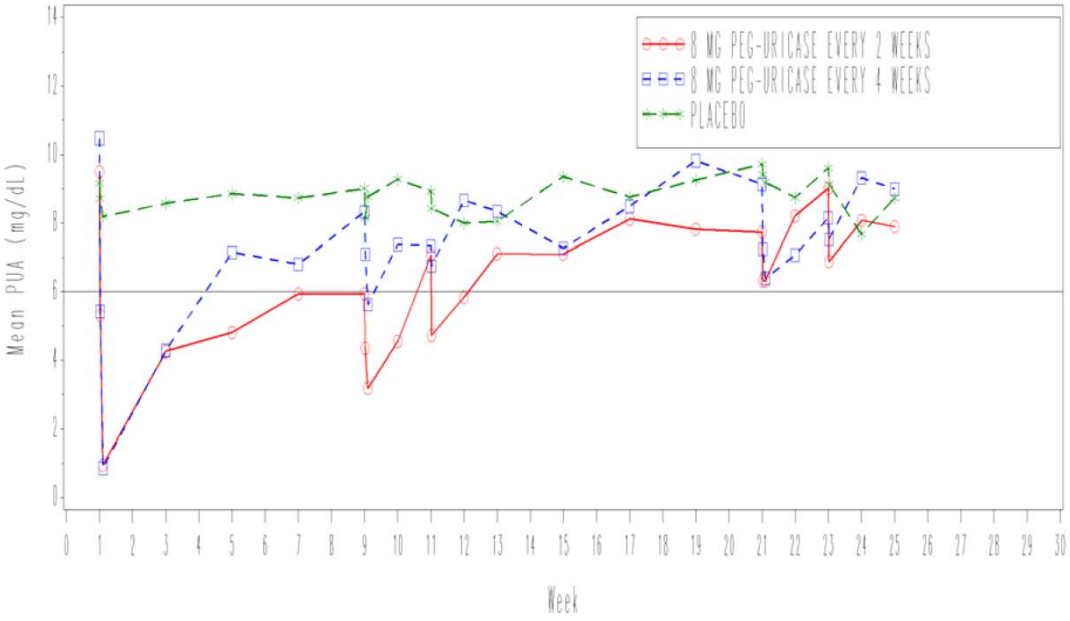
responders over time for the pooled studies by treatment group. These figures graphically illustrate a rapid initial decrease in mean PUA concentration following the administration of the first dose of pegloticase. This response is maintained throughout the remainder of the study by patients who meet the prespecified response criteria as shown in Figure 1. Note that the placebo group does not appear in Figure 1 as there were no responders in the placebo groups in either study. In contrast, patients who were classified as non-responders had an initial drop in plasma uric acid that was subsequently lost (Figure 2).

Figure 1 – Mean PUA Concentration for PUA Responders for Pooled Studies 405 and 406 (ITT Population)



Note: PUA levels which were less than the lower limit of quantitation were interpreted as 0 mg/dL.
Sponsor's Figure 3; p. 62 of ISE

Figure 2 – Mean PUA Concentration for PUA Non-Responders for Pooled Studies 405 and 406 (ITT Population)



Note: PUA levels which were less than the lower limit of quantitation were interpreted as 0 mg/dL.
Sponsor's Figure 3; p. 62 of ISE

Secondary Efficacy Variables

A number of secondary variables were evaluated, as specified in the protocol, based on pooled efficacy data generated from the pivotal Studies 405 and 406. Trends within each study in the secondary endpoints were generally similar to the overall results. No multiplicity correction was planned for in the protocol or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate. The remaining discussion will highlight secondary endpoints of interest.

Mean PUA

As listed in the following table (Table 9), the mean baseline PUA levels for the pooled patients treated with pegloticase every 2 weeks, pegloticase every 4 weeks and placebo were between 9 and 10 mg/dL. Both the pegloticase every 2 weeks and every 4 weeks treatment groups had lower mean PUA levels during Month 3, Month 6, and combined Months 3 and 6 as compared to placebo-treated patients during these time intervals ($p<0.001$ for all comparisons). The mean PUAs for the pegloticase every 2 weeks treatment group were numerically lower than those of the pegloticase every 4 weeks treatment group at each of these prespecified time intervals.

Table 9 – Mean PUA[1] at Month 3, Month 6, and Combined Months 3 and 6 by Treatment Group for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (n=43)
Baseline PUA:			
Number of Subjects	**84**	**83**	**42**
Mean (mg/dL) (SD)	**9.8 (3.0)**	**9.9 (3.1)**	**9.2 (2.8)**
Month 3:			
Number of Subjects	**73**	**74**	**43**
Mean (mg/dL) (SD)	**3.0 (3.3)**	**5.1 (4.0)**	**8.5 (2.3)**
P-Value[2]	**<0.001**	**<0.001**	
Month 6:			
Number of Subjects	**61**	**60**	**40**
Mean (mg/dL) (SD)	**3.2 (4.1)**	**4.9 (3.8)**	**8.8 (2.3)**
P-Value[2]	**<0.001**	**<0.001**	
Months 3 and 6 Combined:			
Number of Subjects	**61**	**60**	**40**
Mean (mg/dL) (SD)	**2.9 (3.6)**	**4.8 (3.7)**	**8.6 (2.0)**
P-Value[2]	**<0.001**	**<0.001**	

[1]Mean PUA: Individual subject mean PUA was defined and calculated as the area under the PUA time curve for each subject divided by the corresponding time interval.
[2]P-value based on two sample t-test to compare corresponding pegloticase group vs. placebo.
Adapted Sponsor's Table 24; p. 67 of ISE.

Tophus Assessments

Patients with tophaceous deposits at baseline had standardized digital photographs of their bilateral hands and feet and up to 2 other sites taken at Weeks 13, 19 and 25. These serial photographs were read by a blinded central reader who assessed them for the size of each target tophus utilizing a validated image analysis software system (MedStudio®). Change from baseline for each measurable tophus (defined as $\geq$ 5mm at baseline in longest dimension with distinguishable borders) was to be scored via a pre-specified 6-point categorical system (e.g., complete response, marked response, partial response, stable disease, progressive disease, and unable to evaluate). Up to 2 unmeasured tophi (e.g., due to location, shape or other factors) were to have been also followed over the course of the study and semi-quantitatively assessed utilizing another 5-point categorical system (e.g., complete response, improved, stable disease, progressive disease, and unable to evaluate). An overall tophus response for each subject based on the best response among all tophi for that subject at a given visit was also determined.

At baseline, 155 subjects in Studies 405 and 406 combined had at least one tophus: 62 subjects in the pegloticase every 2 weeks groups, 64 in the pegloticase every 4 weeks groups, and 29 in the placebo groups. This subset of subjects, the "tophus-evaluable population" is used for the analysis of tophus response while those without tophus at baseline are excluded. Treatment assignment within this subgroup is appropriately random (and thus differences between treatment groups in outcome can be reliably attributed to a treatment effect and not an imbalance in covariates) since the randomizations for each study were stratified by the presence or absence of tophi at baseline. For the pooled data from Studies 405 and 406 at Weeks 13, 19 and 25, significantly higher proportions of patients treated with pegloticase every 2 weeks achieved a complete tophus response compared to placebo-treated patients (p-value $\leq$ 0.002 Table 10). In addition, a significantly greater proportion of patients receiving pegloticase every 2 weeks had a tophus response based on the ordinal (ranked) scores of complete response, partial response, stable disease, and progression of disease compared to placebo-treated patients. Analyses of data for the same outcomes for the pegloticase every 4 week group were not as robust with only a significantly higher proportion of subjects achieving a categorical response at Week 19 as compared to placebo (p=0.004), while the other comparative analyses at the remaining time points showed only positive trends. The overall tophus response analyses from each of the studies independently were similar to each other and to the pooled results.

Table 10 – Assessment of Patient's Overall Tophus Response for Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (N=29)
Week 13			
# of Subjects with Evaluable Tophi	**46**	**48**	**25**
Complete Response	**10 (22%)**	**4 (8%)**	**0 (0%)**
Partial Response	**11 (24%)**	**9 (19%)**	**4 (16%)**
Stable Disease	**20 (44%)**	**28 (58%)**	**13 (52%)**
Progressive Disease	**5 (11%)**	**7 (15%)**	**8 (32%)**
P-Value[1]	**0.002**	**0.068**	
P-Value[2]	**0.011**	**0.292**	
Week 19			
# of Subjects with Evaluable Tophi	**44**	**43**	**26**
Complete Response	**16 (36%)**	**12 (28%)**	**2 (8%)**
Partial Response	**11 (25%)**	**9 (21%)**	**3 (12%)**
Stable Disease	**12 (27%)**	**19 (44%)**	**14 (54%)**
Progressive Disease	**5 (11%)**	**3 (7%)**	**7 (27%)**
P-Value[1]	**0.001**	**0.004**	
P-value[2]	**0.010**	**0.063**	
Week 25			
# of Subjects with Evaluable Tophi	**40**	**42**	**25**
Complete Response	**18 (45%)**	**11 (26%)**	**2 (8%)**
Partial Response	**8 (20%)**	**10 (24%)**	**6 (24%)**
Stable Disease	**10 (25%)**	**16 (38%)**	**11 (44%)**
Progressive Disease	**4 (10%)**	**5 (12%)**	**6 (24%)**
P-Value[1]	**0.002**	**0.061**	
P-value[2]	**0.002**	**0.109**	

[1]An ordinal score was assigned for each response (e.g., Complete Response = 1, Partial Response =2, Stable Disease = 3, and Progressive Disease = 4) and used to compute the P-value, which is based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.
[2]P-value based on Fisher's exact test to compare percent of Complete Response between corresponding pegloticase groups vs. placebo.
Adapted Sponsor's Table 31; p. 74 from ISE

For purposes of analyses for Studies 405 and 406, the time to tophus resolution was specified as the earliest assessment time at which one of the target tophi showed a complete resolution and was based on the tophus-evaluable population. The following table (Table 11) shows a total of 21 subjects from the pegloticase every 2 weeks group, 12 subjects from the pegloticase every 4 weeks group, and 2 subjects from the placebo group who demonstrated resolution of a tophus. The median time to tophus resolution was similar for all three treatment groups: 124 days for the pegloticase every 2 weeks group, 128 days for the pegloticase every 4 weeks group and 137 days for the placebo group.

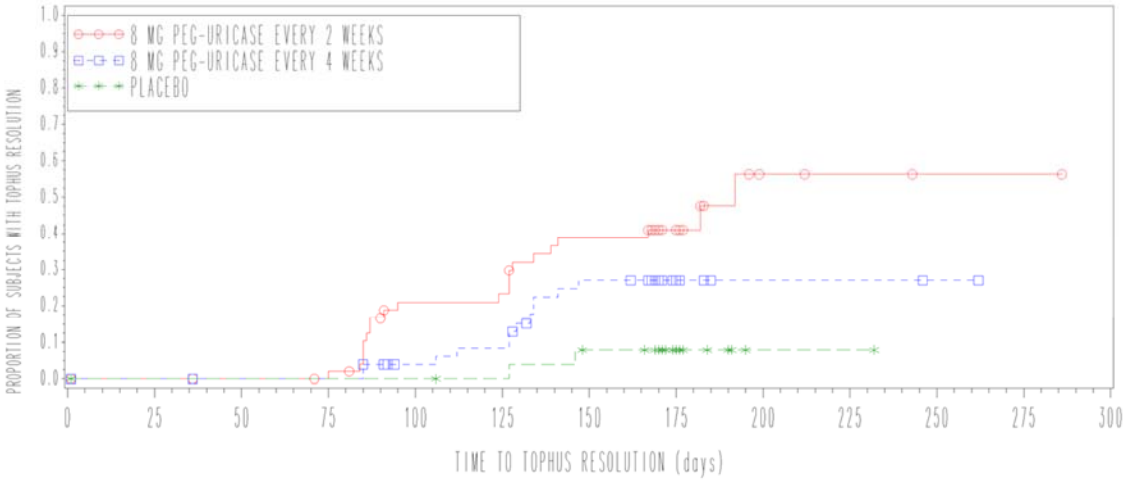
Table 11 – Time to Tophus Resolution for Subjects in Pooled Studies 405 and 406 (Tophus-Evaluable ITT Population)

	Pegloticase q 2 wks (N=62)	Pegloticase q 4 wks (N=64)	Placebo (n=29)
Time to Tophus Resolution[1] (Days)			
Number of Subjects with Resolution of 1 Tophi:	**21**	**12**	**2**
Median	**124 days**	**128 days**	**137 days**
Range (min, max)	**(75, 192)**	**(85, 147)**	**(127, 146)**

Note: Subjects without complete response (CR) at any visit were excluded from the analysis.
[1]Time is calculated as [Visit date of CR – first dose date +1]
Adapted Sponsor's Table 36; p. 83 of ISE.

Figure 3 below shows a Kaplan-Meier plot of the time to complete resolution of tophus in the three treatment groups.

Figure 3 – Kaplan-Meier Plot of Time to Tophus Resolution for Patients Participating in Pooled Studies 405 and 406 (Tophus Evaluable ITT Population)



Note: Censored subjects are represented with symbols.
Sponsor's Fig. 5; p. 84 of the ISE.

Patient Reported Outcomes

The Short Form Health Status Survey (SF-36) and the Health Assessment Questionnaire – Disability Index (HAQ-DI) were the two patient reported outcome measures used to evaluate the clinical consequences of pegloticase therapy. Although 8 domains of the SF-36 were assessed in Studies 405 and 406, only the results from the physical component, mental component and arthritis-specific health index (ASHI) summaries will be presented below. Average scores in an age-corrected, healthy, normal population for males and

females combined for the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were estimated to be 47 and 52, respectively. Table 12 below summarizes the analysis of the results of the responder analyses of the mean PCS scores for the pooled Studies 405 and 406. The baseline PCS scores for all treatment groups were numerically lower than those expected in the general U.S. population. However, there was a baseline imbalance in the PCS scores between treatment arms with higher scores in the pegloticase every 2 weeks group (35.2) than in the placebo group (31.0). At the Week 25 time point, both pegloticase treatment groups showed significantly greater change over baseline than the placebo group ($p<0.001$).

Table 12 – Tabular Summary of the SF-36 Physical Component Summary (PCS) Score for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=85)	**Pegloticase 8 mg every 4 weeks (N=84)**	**Placebo (N=43)**
Baseline Visit:			
Number of Subjects	**83**	**84**	**43**
Mean (SD)	**35.2 (10.9)**	**33.3 (9.8)**	**31.0 (11.1)**
Week 25 :			
Number of Subjects	**61**	**63**	**38**
Mean (SD)	**40.4 (11.3)**	**39.4 (10.6)**	**30.2 (11.9)**
Change From Baseline to Week 25:			
Number of Subjects	**59**	**63**	**38**
Mean (SD)	**6.4 (8.6)**	**5.6 (8.7)**	**-0.87 (8.3)**
P-value[1]	**<0.001**	**<0.001**	**--**

[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 37; p. 91 of the ISE.

The baseline MCS scores for all three treatment groups were similar to each other (range: 47.9 to 49.4) but numerically lower than that expected in the age-matched U.S. population (52) as shown in Table 13. No differences between study arms were seen in the change from baseline to Week 25 in the MCS scores.

Table 13 - Tabular Summary of SF-36 Mental Component Summary (MCS) Score for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit			
Number	**83**	**84**	**43**
Mean (SD)	**49.4 (12.7)**	**45.4 (11.8)**	**47.9 (12.0)**
P-value[1]	**0.523**	**0.259**	
Week 25			
Number	**61**	**63**	**38**
Mean (SD)	**52.7 (10.1)**	**46.8 (12.5)**	**51.3 (10.4)**
P-value[1]	**0.529**	**0.062**	
Change From Baseline to Week 25			
Number	**59**	**63**	**38**
Mean (SD)	**4.2 (10.5)**	**0.67 (10.2)**	**2.4 (8.8)**
P-value[1]	**0.385**	**0.383**	**--**

[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 40; p. 95 of the ISE.

The HAQ-DI assesses disease-related physical function. Scores for this instrument range from 0 to 3 with higher scores indicative of worsening physical function. The mean baseline HAQ-DI scores for all three treatment groups were similar and ranged from 1.1 to 1.24 indicating moderate levels of physical impairment (Table 14). At the week 25 time point both pegloticase treatment groups showed significantly greater improvement over baseline in HAQ-DI than the placebo group ($p = 0.001$).

Table 14 – Health Assessment Questionnaire – Disability Index (HAQ-DI): Physical Function Component Analyses for Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Baseline Visit:			
Number	**83**	**84**	**43**
Mean (SD)	**1.1 (0.86)**	**1.21 (0.86)**	**1.24 (0.95)**
P-value[1]	**0.418**	**0.858**	
Week 25:			
Number	**62**	**63**	**38**
Mean (SD)	**0.84 (0.82)**	**0.85 (0.81)**	**1.31 (0.91)**
P-value[1]	**0.010**	**0.010**	
Change From Baseline to Week 25:			
Number	**60**	**63**	**38**
Mean (SD)	**-0.33 (0.65)**	**-0.25 (0.54)**	**0.08 (0.35)**
P-value[1]	**0.001**	**0.001**	**--**

Note: Scores range from 0 (best) to 3 (worst) and were calculated according to statistical analysis plan (SAP).
[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 46; p. 106 of the ISE.

Pain assessment is a component of the HAQ. Pain is evaluated by patient assessment using a 100 mm visual analogue scale (VAS) where no pain equals a zero score and severe pain equals a 100. Table 15 below summarizes the results of the HAQ assessment of pain for the pooled phase 3 studies. Mean baseline HAQ pain scores were within a comparable range (i.e., 44.2 to 53.9) for all 3 treatment groups. At the Week 25 time point, mean pain scores showed a significant decrease for both pegloticase treatment groups but had increased in the placebo group.

Table 15 – HAQ Assessment of Pain for Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	**Pegloticase q 4 wks (N=84)**	**Placebo (N=43)**
Baseline Visit:			
Number of Subjects	**84**	**84**	**43**
Mean (SD)	**44.2 (28.7)**	**45.1 (27.0)**	**53.9 (28.0)**
P-value[1]	**0.0.66**	**0.087**	
Week 25:			
Number of Subjects	**62**	**63**	**37**
Mean (SD)	**28.4 (25.8)**	**33.1 (27.9)**	**57.2 (27.6)**
P-value[1]	**<0.001**	**<0.001**	
Change From Baseline to Week 25:			
Number of Subjects	**61**	**63**	**37**
Mean (SD)	**-19.4 (29.5)**	**-9.33 (25.8)**	**2.95 (28.3)**
P-value[1]	**<0.001**	**0.029**	**--**

Note: Values range from 0 to 100, where 0 = no pain, and 100 = severe pain.
[1]P-value unadjusted for multiple comparisons from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted from Sponsor's Table 53; p. 113 of ISE.

The Patient Global Assessment (PGA) of the HAQ is also scored by subjects using a 100-mm VAS scale scored where increasing scores are indicative of poorer function. (Note: Spanish speaking patients who participated in this study were not included in the HAQ-PGA assessment since this scale is not included in the validated Spanish HAQ questionnaire.) The following table (Table 16) shows that the baseline HAQ-PGA scores ranged from a low of 42.4 for the pegloticase every 2 weeks group to a high of 51.6 for the placebo group. At the Week 25 time point, mean PGA scores showed a significant decrease for both pegloticase treatment groups consistent with an improvement in PGA but had increased (worsened PGA) in the placebo group.

Table 16– HAQ Patient Global Assessment (PGA) for Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit			
Number	**73**	**78**	**40**
Mean (SD)	**42.4 (24.8)**	**49.8 (24.9)**	**51.6 (24.9)**
P-value[1]	**0.064**	**0.714**	
Week 25			
Number	**52**	**58**	**35**
Mean (SD)	**27.1 (22.6)**	**34.9 (24.7)**	**53.4 (25.5)**
P-value[1]	**<0.001**	**0.001**	
Change From Baseline to Week 25			
Number	**51**	**58**	**35**
Mean (SD)	**-17.5 (24.9)**	**-13.6 (25.5)**	**4.23 (20.2)**
P-value[1]	**<0.001**	**0.001**	**--**

Note: Values range from 0 to 100, where 0 = very well, and 100 = very poor.
[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 56; p. 117 of the ISE.

Number of Swollen and Tender Joints

The arthritic manifestations of gout disease activity were evaluated by conducting swollen and tender joint counts at baseline, Weeks 13, 19 and 25. Table 17 shows that patients had multiple tender and swollen joints at baseline. At Week 25, patients in the pegloticase every 2 week and every 4 week treatment groups showed a greater decrease than placebo in tender joints, in swollen joints and in the number of joints that were either tender or swollen.

Table 17 – Tabular Summary of Analyses of Number of Swollen or Tender Joints of Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 weeks (N=85)	Pegloticase q 4 weeks (N=84)	Placebo (N=43)
Baseline Visit:			
Number of Subjects	**84**	**83**	**43**
Mean (SD)	**20.5 (22.1)**	**21.1 (21.3)**	**27.3 (26.5)**
P-value[1]	**0.130**	**0.159**	
Week 25:			
Number of Subjects	**61**	**63**	**38**
Mean (SD)	**7.1 (12.1)**	**7.8 (11.3)**	**23.3 (26.8)**
P-value[1]	**<0.001**	**<0.001**	
Change From Baseline to Week 25:			
Number of Subjects	**60**	**62**	**38**
Mean (SD)	**-14.9 (20.1)**	**-12.3 (17.2)**	**-2.9 (23.8)**
P-value[1]	**0.009**	**0.025**	

[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 59; p. 121 from ISE.

A clinician's global assessment (CGA) of gout disease activity was included as part of the joint evaluations. The CGA was assessed via a 100 mm VAS with higher scores indicating a bad state. The following table (Table 18) shows that the baseline mean CGA scores were similar between the 3 treatment groups and indicated moderately severe disease. At the Week 25 time point, the pegloticase every 2 weeks group and the pegloticase every 4 weeks treatment group showed a significantly greater decrease in PGA scores than the placebo group ($p < 0.001$ and $p=0.003$, respectively).

Table 18 – Tabular Summary of Analyses of Clinician's Global Assessment (CGA) of Subjects Who Participated in Pooled Studies 405 and 406 (ITT Population)

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Baseline Visit:			
Number	**84**	**83**	**43**
Mean (SD)	**47.6 (28.3)**	**49.7 (28.0)**	**52.6 (28.8)**
P-value[1]	**0.353**	**0.589**	
Week 25:			
Number	**61**	**63**	**38**
Mean (SD)	**16.5 (19.5)**	**21.3 (22.2)**	**43.8 (32.1)**
P-value[1]	**<0.001**	**<0.001**	
Change From Baseline to Week 25:			
Number	**60**	**62**	**38**
Mean (SD)	**-33.9 (25.7)**	**-26.2 (31.2)**	**-8.9 (20.3)**
P-value[1]	**<0.001**	**0.003**	**--**

Note: VAS score ranging from 0 to 100, where 0 = very good to 100 = very bad. This is part of the clinical tender/swollen joint count assessment.
[1]P-value from the two sample t-test that is used to compare means of the corresponding treatment group vs. placebo.
Adapted Sponsor's Table 63; p. 127 from ISE.

Gout Flares

Treatment of gout patients with urate-lowering therapies is associated with an increased risk of gout flare. Despite prophylactic therapy it was expected that some patients may experience gout flares due to the expected fluctuations in PUA levels over the course of Studies 405 and 406 as a result of pegloticase's biological activity. Data regarding these events was analyzed as a secondary endpoint. The incidence and frequency of gout flares reported by the pooled subjects from Studies 405 and 406 during the Months 1 to 3 and Months 4 to 6 were compared by treatment group. Table 19 summarizes the flare incidence for these time intervals. A significantly higher proportion of patients in the pegloticase every 2 weeks (75%) and every 4 weeks (81%) treatment groups experienced flares during Months 1 to 3 as compared to placebo-treated patients (54%) ($p = 0.016$ and $p = 0.002$, respectively). Over the second half of these studies during Months 4 to 6, the opposite was observed with a higher proportion of placebo patients (67%) experiencing gout flares as compared to patients treated with pegloticase every 2 weeks (41%) and pegloticase every 4 weeks (57%). The incidence of flares during Months 4 to 6 for the pegloticase every 2 week group was significantly lower as compared to placebo ($p=0.007$) but was comparable for that of the pegloticase every 4 weeks group and placebo ($p=0.321$).

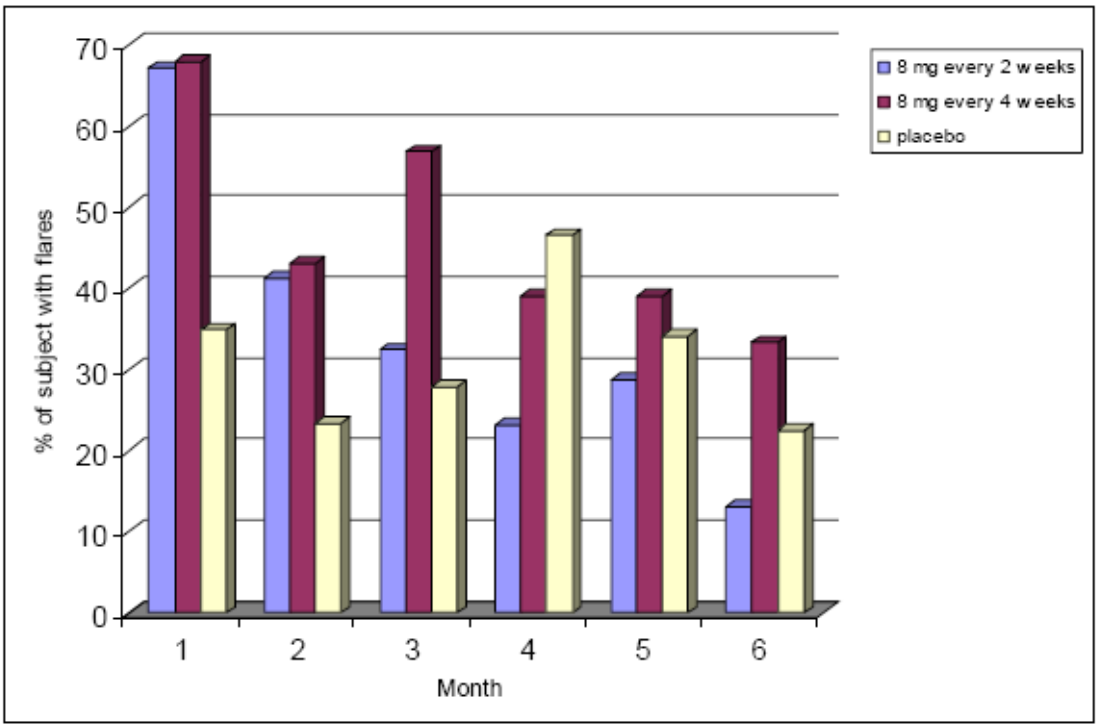
Table 19 – Tabular Summary of Flare Incidence over the Course of Pooled Studies 405 and 406

	Pegloticase 8 mg every 2 weeks (N=85)	Pegloticase 8 mg every 4 weeks (N=84)	Placebo (N=43)
Month 1 to Month 3:			
n/N (%)	**64/85 (75%)**	**68/84 (81%)**	**23/43 (54%)**
P-value[1]	**0.016**	**0.002**	
Month 4 to Month 6:			
n/N (%)	**28/69 (41%)**	**39/69 (57%)**	**29/43 (67%)**
P-value[1]	**0.007**	**0.321**	

Note: "n" represents number of subjects who experienced flares during the periods of interest, Months 1-3 and Months 4-6. "N" represents total number of subjects with at least one visit during the periods of interest.
[1]P-value using Fisher's exact test used to compare number of responders reporting flares.
Adapted Sponsor's Table 66; p. 133 of the ISE.

The following figure (Figure 4) graphically depicts the incidence of gout flares on a monthly basis over the course of the pooled phase 3 studies by treatment group. As described above, a higher percentage of patients in both pegloticase treatment groups experienced gout flares during the first 3 months of the trials. Starting at Month 4, the incidence of gout flares for the pegloticase every 2 week treatment group fell to below that of the placebo group, and continued to remain lower during Months 5 and 6. In contrast, the incidence of flares for the pegloticase every 4 week group fell during Months 5 and 6 as compared to earlier time points, but remained higher than that of the placebo group during these time points.

Fig. 4 – Incidence of Flares at Each Month by Treatment Group for Pooled Studies 405 and 406 (ITT Population)



Sponsor's Fig. 14; p. 131 of the ISE

Severity of gout flares was also examined (Table 20 below). Over the course of these pooled pivotal studies, 60% of the placebo group reported their gout attacks as moderate-to-severe in nature as compared to 68% of the patients in the pegloticase every 2 weeks group and 70% of patients in the pegloticase every 4 weeks group. During the first half of these studies (Months 1-3), 30% of the placebo subjects reported having moderate-to-severe flares of gout as compared to 65% of subjects in the pegloticase every 2 weeks and 64% of subjects in the pegloticase every 4 weeks treatment groups. With prolonged exposure to pegloticase, the number of patients who reported moderate-to-severe attacks during Months 4-6 decreased to 25% for the pegloticase every 2 weeks group and 39% for the pegloticase every 4 weeks group as compared to 49% of placebo treated patients.

Table 20 – Tabular Summary of Patients with Gout Flares by Severity for the Pooled Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
During Study Period[1]			
Number of Patients[2]	85	84	43
None	20 (24%)	14 (17%)	8 (19%)
Mild	7 (8%)	11 (13%)	9 (21%)
Moderate	37 (44%)	38 (45%)	20 (47%)
Severe	21 (25%)	21 (25%)	6 (14%)
Months 1-3			
Number of Patients[2]	85	84	43
None	22 (26%)	16 (19%)	21 (49%)
Mild	7 (8%)	14 (17%)	9 (21%)
Moderate	37 (44%)	35 (42%)	11 (26%)
Severe	19 (22%)	19 (23%)	2 (5%)
Months 4-6			
Number of Patients[2]	69	69	43
None	41 (59%)	30 (44%)	14 (33%)
Mild	11 (16%)	12 (17%)	8 (19%)
Moderate	12 (17%)	21 (30%)	15 (35%)
Severe	5 (7%)	6 (9%)	6 (14%)

Note: Missing severity response for gout flare was imputed as severe unless the subject experienced another occurrence within the same period for which severity was recorded.
Note: If the same subject in a given treatment had more than one occurrence, only the most severe occurrence was taken.
[1]During the study period = first dose to 4 weeks after last dose
[2]N represents the number of subjects who had a visit within each time period.
Sponsor's Table 69; p. 135.

Efficacy Conclusions

The efficacy of pegloticase administered at doses of either 8 mg every 2 weeks or 8 mg every 4 weeks as intravenous infusions in the treatment of uncontrolled hyperuricemia for the management of the signs and symptoms of treatment failure gout was assessed in two randomized, placebo-controlled replicate Phase 3 trials, Studies 405 and 406. In both studies, normalization of PUA to < 6 mg/dL during Months 3 and 6 was achieved by a significantly greater proportion of patients administered either pegloticase 8 mg every 2 weeks or 8 mg every 4 weeks as compared to placebo. The magnitude of the decrease in mean PUA levels was greater in both pegloticase treatment groups as compared to placebo. In addition to lower plasma urate levels, patients treated with pegloticase had a significant reduction in tophi (for those with at least one tophus at baseline), reduction in swollen and tender joints, and a decrease in the frequency and severity occurrence of gout flares among patients who received pegloticase every 2 weeks as compared to placebo. Although the results of some of these secondary assessments (e.g., resolution of tophi and number of swollen and tender joints) trended toward improvement in the pooled analyses of patients who received pegloticase every 4 weeks, unlike the results for the pegloticase

every 2 weeks, they did not achieve significance as compared to placebo. The incidence of gout disease flares in the pegloticase every 4 weeks dose group was comparable to that of placebo treated patients and was also observed to be higher than placebo during the last 4 months of the study. Patients receiving pegloticase every 2 or 4 weeks achieved significant improvements in function and pain as assessed by the SF-36 PCS, HAQ-DI, pain assessment, PGA and CGA relative to subjects receiving placebo.

Safety

This application contained 24-week, randomized, blinded safety data generated from the 2 pivotal trials 405 and 406 (Table 1, above). In addition there were safety data generated from the ongoing 48-week open-label extension Study 407, and single dose and 12-week multiple dosing data from the Phase 1 and Phase 2 trials (Studies 401, 402 and 403). Since the safety data from Studies 401, 402 and 403 were associated with a different route of administration (e.g., subcutaneous injection), or doses and regimens not under consideration for marketing, these data are only considered where pertinent in the discussion that follows. In general terms the Agency identified several areas of potential concern: a higher rate of serious cardiovascular adverse events in the pegloticase-treated patients, infusion reactions and the development of antibodies to pegloticase in some patients (immunogenicity) with impacts on safety and efficacy.

Exposure

At the time of the initial submission, the extent of exposure to either the 8 mg every 2 week or 8 mg every 4 week pegloticase dosing regimens for the multiple dosing Studies 403, 405, 406 and 407 was as shown in Table 21 below. The median number of infusions for the every 2 week dose regimen proposed for marketing was 19 with a total of 1972 infusions administered overall. The median study duration for subjects who received 8 mg every 2 weeks of pegloticase was 327 days and 286 days for those subjects who received 8 mg every 4 weeks. A combined total of 101 patients from both pegloticase dose groups had exposure for at least 12 months, out of which 27 patients had exposure for at least18 months. With the 120-day safety update, these numbers increased to 121 patients from both pegloticase dose groups with exposure for at least 12 months and 95 patients with exposure for at least 18 months.

Ordinarily for a product intended for chronic use, the ICH E1A guideline would apply with respect to the size of the safety database. The ICH E1A guidance document specifies a safety database of 1500 patients treated overall, 300-600 treated for at least 6 months and 100 treated for at least 1 year. However, ICH E1A guidelines do not apply to orphan disease indications and pegloticase has orphan status for treatment of refractory gout. For orphan diseases the size of the target patient population should be taken into account when deciding on the appropriate size of the safety database.

Table 21 – Summary of Number of Pegloticase Infusions and Study Duration for Subjects Who Received Multiple Doses of Pegloticase in the Phase 2 and 3 Trials (Studies 403, 405, 406 and 407)

	Pegloticase 8 mg q 2 wks (N=116)	Pegloticase 8 mg q 4 wks (N=113)
Number of Pegloticase Infusions per Subject		
Mean (SD)	17 (11)	11 (9)
Median (Min, Max)	19 (1, 38)	8 (1, 32)
Study Duration (Days)[1]		
Mean (SD)	316 (172.2)	306 (182.2)
Median (Min, Max)	327 (29, 658)	286 (1, 623)
Study Duration (Weeks)		
Up to 4 Weeks	0	2 (2%)
4-8 weeks	6 (5%)	4 (4%)
8-12 weeks	4 (3%)	6 (5%)
12-16 weeks	7 (6%)	5 (4%)
16-20 weeks	4 (3%)	12 (11%)
20-28 weeks	17 (15%)	14 (12%)
28-36 weeks	12 (10%)	9 (8%)
36-44 weeks	3 (3%)	7 (6%)
44-52 weeks	10 (9%)	6 (5%)
52-64 weeks	25 (22%)	14 (12%)
64-77 weeks	15 (13%)	20 (18%)
>77 weeks	13 (11%)	14 (12%)

Note: Number of infusions excludes placebo infusions.
[1]For subjects enrolled in Studies 405 or 406 with initial pegloticase treatment, the study duration is defined as the sum of study durations in the double-blind studies (405 or 406) and open-label study (407). However, for subjects with placebo treatment in Studies 405 or 406, only the study duration in 407 is included in the summary.
Adapted Sponsor's Tables 11 and 12; p. 42-43 of ISS

Overview of Safety

All safety analyses were performed on the population who received at least 1 infusion of study medication. Table 22 summarizes adverse events (AEs) that were reported in the pegloticase safety database presented as pooled safety data from the 2 controlled trials (Studies 405 and 4060) by treatment group as well as cumulative adverse event data collected from patients who completed these studies and continued to receive pegloticase through their participation in the ongoing open-label extension (OLE) Study 407. Safety data collected from patients who had previously received placebo during the controlled studies and initiated pegloticase therapy in the OLE was also reviewed and will be discussed as pertinent. The majority of subjects (over 90% in each of the study arms) in the pivotal pegloticase studies experienced at least 1 AE during their participation in these studies.

Table 22 –Tabular Summary of Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares Reported by Subjects by Treatment Group for the Pooled Controlled Studies 405 and 406 and Open-Label Extension Study 407

	6-Month Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number Of Adverse Events (AE)	370	693	870	1044	1411
Number of Subjects with AEs	41 (95%)	80 (94%)	84 (100%)	83 (98%)	84 (100%)
Number of Subjects with Serious AEs (SAE)	5 (12%)	20 (24%)	19 (23%)	24 (28%)	27 (32%)
Number of Subjects with Infections	22 (51%)	30 (35%)	40 (48%)	41 (48%)	54 (64%)
Number of Subjects with Serious Infections	4 (9%)	3 (4%)	5 (6%)	3 (4%)	7 (8%)
Number of Subjects with Malignancy	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Number of Subjects with Infusion Reactions (IR)	2 (5%)	22 (26%)	34 (41%)	26 (31%)	38 (45%)
Number of Subjects Who Discontinued Due to AEs	1 (2%)	16 (19%)	17 (20%)	18 (21%)	21 (25%)
Deaths	1 (2%)	3 (4%)	1 (1%)	0 (0%)	2 (2%)

Note: Except for the "Number of AEs", subjects are counted only once in each row.
Adapted Sponsor's Tables 24, 37, 40 and 69; p.56, 79, 81 and 127, respectively of the ISS.

Controlled data from the 6-month studies show that treatment with pegloticase was associated with a higher rate of serious adverse events (SAEs). The proportions of patients in the pegloticase every 2 week (24%) and every 4 week (23%) groups who developed an SAE were comparable but were higher than in the placebo group (12%). With prolonged exposure, the incidence of SAEs increased slightly for both dose groups of pegloticase-treated patients. The proportion of patients who experienced an infection or a serious infection during the controlled studies was not increased in the pegloticase groups compared to the placebo group. Overall, the number of cases of malignancies in this safety database was low and did not increase with prolonged exposure. Since pegloticase is a non-human protein there is the potential for developing an antibody response to the product, which could manifest as an infusion reaction. In fact the proportion of patients experiencing an infusion reaction was increased in the pegloticase-treated patients compared to controls in spite of the standardized pre-treatment prophylaxis regimen (26% and 41% in the two pegloticase study arms versus 5% in the placebo group). Notably the rate of infusion reactions was lower in the group receiving more frequent infusions (every 2 weeks, 26%) than in patients receiving less frequent infusions (every 4 weeks, 41%). Most of the patients who had an infusion reaction had it in the first 6 months of treatment. However, some additional cases were observed after 6 months.

During the controlled studies, the proportions of patients who experienced an AE leading to withdrawal were similar for both pegloticase treatment groups (19-20%) but were much higher as compared to placebo (1%). These proportions slightly increased with

increasing duration of exposure. More deaths occurred during the controlled studies with a higher proportion occurring in the pegloticase every 2 weeks treatment group (3/85, 3%) as compared to the pegloticase every 4 week (1/85, 1%) and placebo group (1/43, 1%). These deaths and the 2 deaths that occurred during the OLE study will be further discussed below.

Deaths

There were a total of 9 deaths reported in the pegloticase clinical development program as follows: 3 deaths in the pegloticase every 2 weeks group, 3 deaths in the pegloticase every 4 weeks group, and 3 deaths in the placebo group. (Note: Two deaths occurred more than 30 days after the last dose of study drug was administered; a tabular summary of all 9 deaths can be found in the appendix.) Two of the 3 deaths that occurred in patients receiving pegloticase every 2 weeks (Subjects 405-203-001 and 406-315-005) were due to sudden death in patients with histories of extensive cardiovascular disease including end-stage cardiomyopathy (ejection fraction of 17%), congestive heart failure (CHF), coronary atherosclerotic heart disease and coronary artery bypass. Additionally, both of these patients had multiple other comorbid conditions that increased their risk for developing a fatal cardiovascular event. The third subject who died in the pegloticase every 2 weeks group (Subject 406-301-003) was an 89-year-old male resident of a nursing home who developed an infected perianal decubitus ulcer from sleeping in a chair. Subsequently, he died of sepsis secondary to methicillin-resistant staphylococcus aureus (MRSA) after refusing additional invasive medical treatment for his infection after failing extensive antibiotic therapy.

Two of the 3 deaths in the pegloticase every 4 weeks group occurring in patients during the open-label extension were also due to sepsis. Both of these patients (Subjects 407-122-004 and 406-325-001) had originally received pegloticase every 2 weeks while in the controlled studies, but opted to switch to the every 4 week dose regimen prior to entering the open-label extension trial. Subject 407-122-004, a 53-year-old female, had developed oxacillin-resistant staphylococcus aureus (ORSA) osteomyelitis of her right first metatarsophalanx (MTP) that resulted in the amputation of her toe. She subsequently became septic despite antibiotic therapy and died following removal of life support after failing to respond to aggressive medical management and therapy. The other patient who died due to sepsis in the pegloticase every 4 weeks group was a 63-year-old male (Subject 406-325-001) who developed necrotizing skin lesion on his face and hands approximately 4 weeks after receiving his last dose of study medication. Since these lesions were not considered to be of infectious origin, he was treated with a course of 60 mg a day of prednisone pending the results of a skin biopsy and cultures of these lesions. He was hospitalized 1 week later for treatment of septic shock and renal failure after developing cellulitis of his left arm and died following the removal of life support after failing to respond to aggressive medical treatment. Cultures of the skin lesions grew out both streptococcus and staphylococcus and were supported by the histopathology results from the skin biopsy which were consistent with an ongoing infectious process. The third patient who died in the pegloticase every 4 week group was a 64-year-old male with

end-stage cardiomyopathy (ejection fraction of 10-15%), CHF, coronary artery disease, atrial fibrillation, and status post pacemaker insertion who did not disclose his full medical history at the time of study enrollment (protocol violation). He was hospitalized a day after receiving his second study infusion for the treatment of acute dsypnea secondary to CHF. He developed acute renal failure during his hospitalization that required dialysis. This patient's death was the result of renal failure after he refused additional dialysis treatments.

Of the three patients who died in the placebo group, one patient (Subject 406-301-014) died post-randomization prior to receiving a dose of study medications. The remaining 2 patients (Subjects 405-101-005 and 406-311-002) died 4 months after receiving their scheduled study infusions. These two patients withdrew from the study after either being lost to follow up post-hospitalization for treatment of urosepsis and a severe gout flare and a recurrence of CLL, respectively. Both of these deaths were attributed to the patients underlying medical conditions (i.e., cardiac disease and CLL).

In considering the deaths occurring in the pegloticase clinical development program it is important to consider which events may be related to the drug and which to concomitant conditions. In that regard it is clear that the patient population enrolled in the studies is at increased risk of mortality as shown by the occurrence of one death in a randomized patient in the short time before the first dose of study medication and by the occurrence of 2 additional deaths in the placebo group 4 months after their last placebo infusion. In addition, it is also clear that many of the deaths occurred in patients with comorbidities that predispose to serious cardiovascular events and infections including advanced congestive heart failure, diabetes mellitus, hypertension and renal failure.

Serious Adverse Events

During the controlled studies, a higher proportion of patients experienced SAEs in the pegloticase every 2 week (24%) and every 4 week group (23%) than in the placebo group. (Note: For a complete tabular listing of SAEs categorized by system organ class see Table 39 in the appendix.) Three system organ classes contributed to the higher overall rates of SAEs in the pegloticase groups: general disorders and administration site conditions, musculoskeletal and connective tissue disease, and cardiac disorders.

The higher rate of SAEs seen in the musculoskeletal and connective tissue disease conditions in the pegloticase every 2 week group is attributable to single cases of hemarthrosis, steroid myopathy, osteoarthritis and synovial cyst, none of which have a clear relationship to study drug. Rather they appear related to concomitant medical conditions and concomitant medications. Table 23 below highlights the SAE profiles for the other two remaining system organ classes. Review of these data show that the higher rates of SAEs observed in the general disorders and administration site conditions for the pegloticase treatments are primarily due to infusion reactions, which are an expected adverse event associated with the product due to its immunogenicity.

The higher rates of cardiac disorders reported in the pegloticase every 2 weeks (5%) and every 4 weeks (4%) treatment groups as compared to placebo (0%) were unexpected and will be discussed further with other safety areas of interest. Review of the 24 SAEs (14 SAEs in the pegloticase every 2 weeks group and 10 SAEs in the pegloticase every 4 weeks group) contained in the 120-day safety update that occurred in patients participating in the ongoing OLE study showed that they were similar to what had been observed during the controlled studies, and did not indicate any additional potential safety signals.

Table 23 –Number (%) of Subjects with Serious Adverse Events (SAEs) Including Infusion Reactions and Gout Flares in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

Adverse Event Via MedDRA System Organ Class (SOC) and Preferred Term	6-Month Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number of SAE	**14**	**34**	**30**	**45**	**50**
Number (%) of Subjects with SAE	**5 (12%)**	**20 (24%)**	**19 (23%)**	**24 (28%)**	**27 (32%)**
Gen. Disorders and Adm. Site Condit.:	**0 (0%)**	**7 (8%)**	**7 (8%)**	**10 (12%)**	**10 (12%)**
Infusion Related Reaction	0 (0%)	4 (5%)	7 (8%)	5 (6%)	8 (10%)
Chest Pain	0 (0%)	1 (1%)	0 (0%)	2 (2%)	1 (1%)
Peripheral Edema	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pyrexia	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Adverse Drug Reaction	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Asthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Cardiac Disorders:	**0 (0%)**	**4 (5%)**	**3 (4%)**	**4 (5%)**	**3 (4%)**
Arrhythmia	0 (0%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Angina Pectoris	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Cardiac Arrest	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Congestive Cardiac Failure	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Tachycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Note: If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once.
Adapted Sponsor's Tables 34; p. 72-3 and Table B8.3 in Appendix of ISS.

Adverse Events of Special Interest

a. Cardiac

Due to an imbalance in the number of serious cardiac adverse events between study arms (Table 24), further examinations of the safety database were undertaken by both the Applicant and the Agency. As shown in the table the imbalance reflects various different types of events, including 2 cases of arrhythmia and single cases of tachycardia, congestive heart failure, cardiac arrest, MI and angina pectoris.

Table 24 - Cardiac Serious Adverse Events (SAEs) via MedDRA Preferred Terms for the Pooled Safety Database from Controlled Studies 405 and 406 by Sponsor

MedDRA Preferred Term	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number (%) of Subjects with Cardiac SAEs	**4 (5%)**	**3 (4%)**	**7 (4%)**	**0 (0%)**
Ischemic Cardiovascular Disease:				
Cardiac Arrest	1	0	1	0
Myocardial Infarction	0	1	1	0
Angina Pectoris	0	1	1	0
Heart Failure:				
Congestive Cardiac Failure	1	0	1	0
Cardiac Arrhythmias:				
Arrhythmia	2	0	2	0
Tachycardia	0	1	1	0

Adapted from Sponsor's Table 34; p. 72-3 of ISS.

During the FDA's review of the pegloticase application, the Applicant submitted an amendment with the findings of an independent blinded cardiovascular adjudication committee that conducted a post hoc review of all possible cardiovascular events from the pegloticase Phase 2 (Study 403), Phase 3 (Studies 405 and 406) and the ongoing open-label extension (Study 407) trials. The committee used the following definitions in their analysis of these data:

1. Anti-Platelet Trialist Collaborative (APTC) Events
    a. Non-fatal myocardial infarction
    b. Non-fatal stroke
    c. Cardiovascular deaths
2. Non-APTC Major Adverse Cardiovascular Events (MACE)
    a. Unstable angina (includes acute coronary syndrome)
    b. Coronary revascularization
    c. Transient ischemic attacks

Table 25 summarizes the results of this analysis as it pertains to data from the double-blind portion of Studies 405 and 406.

Table 25 – Analyses of Subjects with Major Cardiac Adverse Events by Sponsor's Cardiac Event Adjudication Committee for the Pooled Safety Database from the Controlled Studies 405 and 406

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)	Placebo (N=43) n (%)
Number (%) of Subjects with Major CV Events	**4 (5%)**	**6 (8%)**	**10 (6%)**	**0 (0%)**
All APTC* Events:	**2 (2%)**	**1 (1%)**	**3 (2%)**	**0 (0%)**
Cardiovascular Deaths	2	0	2	0
Non-Fatal Myocardial Infarction	0	1	1	0
Non-Fatal Stroke	0	0	0	0
Non-APTC CV Events:	**2 (2%)**[**]	**5 (6%)**	**8 (5%)**	**0 (0%)**
Angina	0	1	1	0
Congestive Heart Failure	2	1	3	0
Arrhythmia	1	1	2	0
Deep Venous Thrombosis	0	1	1	0
Transient Ischemic Attack	0	1	1	0

* Anti-Platelet Trialist Collaborative

** Two subjects had multiple events: Subject 406-311-005 had 2 events (CHF and arrhythmia); Subject 405-122-003 had both an APTC event (MI) and a non-APTC event (DVT).

The overall rates of both APTC events and non-APTC events are comparable for both pegloticase treatment groups but higher as compared to the placebo treatment group. In terms of non-APTC events, there were 3 subjects (2%) in the pegloticase every 2 weeks group, 5 subjects (6%) in the pegloticase every 4 weeks group and none in the placebo group. Based on the above data, no meaningful conclusions were drawn by this committee due to the small sample size and skewed randomization (i.e., 2:2:1).

An internal consultant from the Agency's Division of Cardiovascular and Renal Drug Products also reviewed these data. Table 26 summarizes the findings of this review. (Note: A copy of this review by Dr. Stephen M. Grant dated February 19, 2009 is included in the appendix of this document.) Based on the Dr. Grant's analysis of these data, there were a total of 5 (6%) major cardiac AEs that occurred in the pegloticase every 2 weeks group, 3 (4%) events in the every 4 week group, and 1 (2%) event in the placebo group. All of these events occurred in patients who had pre-existing comorbid risk factors for the development of major cardiac adverse events. The occurrence of these events is not unexpected given the high prevalence of underlying cardiovascular disease in the patient population who participated in these trials. Dr. Grant concluded that the distribution of cardiovascular deaths and of cardiac SAEs due to ischemic vascular disease and/or heart failure was not obviously unusual even considering the decreased duration of exposure in the pegloticase treatment arms due to more pegloticase-treated subjects withdrawing prior to study conclusion. However, there remains a degree of uncertainty about the cardiac safety of pegloticase because so few events were observed due to the limited number of subjects enrolled and limited duration of follow-up.

Table 26 –Analyses of Subjects with Major Cardiac Adverse Events Experienced by Patients for the Pooled Safety Database for the Controlled Studies 405 and 406 as Attributed by FDA

Major Cardiac Adverse Events	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Total Pegloticase (N=169)	Placebo (N=43)
Number of Subjects with Major Cardiac AEs:	**5 (6%)**	**3 (4%)**	**8 (5%)**	**1 (2%)**
Ischemic Cardiovascular Disease:				
Sudden Death	2	0	2	0
Inferiolateral Myocardial Infarction	0	1	1	0
"Troponin Leak"	0	0	0	1
Transient Ischemic Attack	0	1	1	0
Heart Failure:				
Heart Failure	2	0	2	0
Cardiac Arrhythmias:				
Supraventricular Tachycardia	0	1	1	0
Ventricular Tachycardia	1	0	1	0

In order to better assess the cardiovascular safety of pegloticase, outlier and quartile analyses for changes in both blood pressure (> 20 mm Hg) and pulse rate ($\geq$ 100 bpm), as well as examination of electrocardiographic abnormalities identified on the final electrocardiograms of subjects enrolled in Studies 405 and 406 consistent with myocardial infarction or prolongation of the QT interval were undertaken. These analyses did not identify any additional safety signals. However, these retrospective analyses are limited and should not be considered exculpatory because only very large differences among subjects in the treatment groups could have been detected. The measurement of blood pressure and QT interval in studies 405 and 406 was performed neither frequently nor carefully enough to have detected smaller but clinically important changes.

Review of the 120-day safety data update identified an additional 2 case reports of SAEs of cardiac origin. One of these events occurred in a 52-year-old male patient (Subject 405-120-001) who had a myocardial infarction one day after receiving his pegloticase every 4 weeks study infusion. This patient had a history of hyperlipidemia but no other risk factors for coronary atherosclerosis. The second case occurred in a patient (Subject 406-307-006) with known ischemic heart disease with an implanted cardiodefibrillator and pacemaker who was receiving pegloticase infusions every 2 weeks that was hospitalized for treatment of congestive heart failure. One other SAE of cardiac origin was identified on search of the safety database for the Phase 1 and 2 studies. The patient was a 77-year-old female (Subject 403-002-003) with a history of coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, pulmonary embolus and deep venous thrombosis who had a transient ischemic attack (TIA) 4 weeks following the administration of her second dose of pegloticase 12 mg every 4 weeks in the Phase 2 dose ranging study (Study 403). This patient recovered from her TIA and continued in the study.

b. Hematological

Since one of the byproducts of pegloticase's enzymatic breakdown of uric acid is hydrogen peroxide, a safety concern regarding the development of hemolytic anemias and other hematological adverse events was raised. The Applicant excluded G6PD-deficient patients from the trials and proposes that these patients should not use the product if pegloticase is marketed. Table 27 summarizes the MedDRA preferred AE term for hematological AEs that occurred during the controlled Studies 405 and 406 as well as during the open-label extension, Study 407. Overall, these proportions were similar for the 3 treatment groups and with prolonged exposure to the product. Further review of these data does not identify any pattern of hematologic AEs that were either dose-associated or associated with prolonged exposure to pegloticase.

Table 27 - Number (%) of Subjects with Hematological Adverse Events via MedDRA Preferred Term by Treatment Group in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

MedDRA System Organ Class Collapsed Preferred AE Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Hematological	**5 (12%)**	**12 (14%)**	**7 (8%)**	**12 (14%)**	**9 (11%)**
Anemia	4 (9%)	7 (8%)	4 (5%)	7 (8%)	5 (6%)
Neutropenia	0 (0%)	2 (2%)	1 (1%)	1 (1%)	0 (0%)
Febrile Neutropenia	1 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Increased Hematocrit	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Leukocytosis	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Leukopenia	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Thrombocythemia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Thrombocytopenia	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Red Cell Count Decreased	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)

Note: If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once.
Adapted Sponsor's Table A8.2, Appendix 23.2 from Hematologic section and Table B8.2 Appendix from Hematologic section of the ISS.

c. Allergic Manifestations

Due to concerns raised by the occurrence of urticaria seen with subcutaneous injection in Study 401 and the immunogenicity profile of pegloticase, the safety database was searched for hypersensitivity-type allergic AEs (Table 28). Overall, there were more allergic AEs in the pegloticase treatment arms (28% and 51%) than in the placebo arm (16%). Most of the cases were characterized as infusion-related reactions. In addition, there were 2 cases of urticaria reported in both the pegloticase every 2 weeks and every 4 weeks treatment groups as compared to none in the placebo group. There was 1 case of angioedema in a patient who received pegloticase every 4 weeks as compared to none in the pegloticase every 2 weeks and placebo groups. With prolonged exposure no new

cases of angioedema or urticaria were observed in the open-label extension or in the 120-day safety update.

Table 28 – Number (%) of Subjects with Allergic Adverse Events via MedDRA Preferred Term by Treatment Group in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

MedDRA System Organ Class Collapsed Preferred AE Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Allergic	**7 (16%)**	**24 (28%)**	**43 (51%)**	**30 (35%)**	**49 (58%)**
Infusion-Related Reaction	2 (5%)	22 (26%)	35 (42%)	26 (31%)	39 (46%)
Rash	3 (7%)	2 (2%)	3 (4%)	5 (6%)	5 (6%)
Urticaria	0 (0%)	2 (2%)	2 (2%)	2 (2%)	2 (2%)
Rash Macular	1 (2%)	2 (2%)	0 (0%)	2 (2%)	1 (1%)
Seasonal Allergy	0 (0%)	0 (0%)	3 (4%)	0 (0%)	3 (4%)
Wheezing	0 (0%)	0 (0%)	3 (4%)	0 (0%)	3 (4%)
Drug Hypersensitivity	1 (2%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Rash Papular	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Angioneurotic Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Face Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Rash Generalized	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash Maculo-Papular	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rhinitis Allergic	0 (0%)	0 (0%)	1 (1%)	1 (1%)	3 (4%)
Throat Tightness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Note: If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once.
Adapted Sponsor's Table A8.2, Appendix 23.2 from Allergic section and Table B8.2 Appendix 23.4 from Allergic section of the ISS.

The allergic adverse events shown in Table 28 exclude similar types of events that occurred as a component of an infusion-related reaction. Since the majority of allergic AEs were attributed to infusion-related reactions, defined by the Applicant as a cluster of AEs that occurred during or within 2 hours after the end of the study medication infusion, additional examination of these component events was undertaken and is presented in the next section in Table 31. Although some of the component events associated with infusion-related reactions should be classified as hypersensitivity type reactions (i.e., urticaria, rash, throat tightness, and wheezing) they were attributed as components of infusion reactions due to the timing of their appearance.

d. Infusion Reactions

The majority of patients who receive pegloticase develop at least some level of antibodies to the product, raising a concern for allergic reactions and infusion reactions. To limit the occurrence of hypersensitivity and infusion reactions observed during the Phase 1 and Phase 2 studies, all patients received a standard pre-treatment prophylaxis regimen

consisting of 60 mg fexofenadine the night before followed in the morning by another dose of 60 mg of fexofenadine with 1000 mg acetaminophen, and 200 mg of hydrocortisone IV immediately prior to each infusion. In addition to supportive medical care and monitoring, the management of infusion reactions included the slowing or stopping of the infusion followed by either restarting the study infusion more slowly or discontinuing it, with or without the administration of fluids, diphenhydramine, or corticosteroids depending on the severity of the reaction. However, one patient (Subject 406-319-004) did require treatment with 1 dose of epinephrine for a moderate infusion reaction characterized by flushing, diaphoresis, shortness of breath, light headedness and rash but recovered without sequelae. Five other patients were sent to the emergency room for additional monitoring after experiencing moderate-to-severe infusion reactions but they also recovered without sequelae. Table 29 summarizes the number and severity of infusion reactions observed during the controlled Studies 405 and 406 and the open-label extension Study 407. The proportion of infusion reactions was highest in patients treated with pegloticase every 4 weeks (41%) as compared to every 2 weeks (26%) versus placebo (5%). With prolonged exposure these rates increased to 45% for the pegloticase every 4 weeks group and 31% for the pegloticase every 2 weeks group. Review of the data contained in the 120-day safety update revealed that these rates remained comparable with increasing duration of product exposure (49% and 29%). In terms of severity of these AEs, 36% of patients reported having moderate-to-severe infusion reactions in the pegloticase every 4 weeks treatment group as compared to 18% of patients in the pegloticase every 2 weeks group and 5% in the placebo. Review of the data in the 120-day safety update regarding the proportion of patients with moderate to severe infusions reactions with increasing duration of exposure were comparable to earlier data (40% and 23% for the every 4 week group and every 2 weeks group, respectively).

Table 29 – Number (%) of Patients Experiencing Infusions Reactions by Severity for Pooled Controlled Studies 405 and 406 and OLE Study 407

Infusion Reaction Severity	6-Month Pooled Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number (%) of Infusion Reactions	**2 (5%)**	**22 (26%)**	**34 (41%)**	26 (31%)	38 (45%)
Mild	0	7 (8%)	4 (5%)	7 (8%)	56%)
Moderate	2 (5%)	11 (13%)	22 (26%)	14 (17%)	24 (29%)
Severe	0	4 (5%)	8 (10%)	5 (6%)	9 (11%)

Note: An infusion reaction is an event or cluster of events that occurred during or within two hours after an infusion. Missing severity response for infusion reaction was imputed as "Severe" if there was no infusion reaction reported on a prior dose visit. Otherwise, prior severity was carried forward.
Adapted Sponsor's Table 91; p. 178 and Table B11.3 Appendix of ISS

Table 30 summarizes the occurrence of infusion reactions by dose and pooled treatment group during the controlled studies. The rate of occurrence of infusion reactions peaked

at Dose 3 (44%) for the pegloticase every 4 week group and at Dose 4 (23%) for the pegloticase every 2 week and decreased thereafter.

Table 30 – Number (%) of Patients Who Experienced an Infusion Reaction[1] by Treatment Group and Dose Number for Pooled Controlled Studies 405 and 406

Infusion Reaction Reported at:	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	All Pegloticase (N=169)
Number (%) of Subjects with First Infusion Reaction at:				
Dose 1	1 (50%)	1 (5%)	4 (12%)	5 (9%)
Dose 2*	NA	4 (18%)	1 (3%)	5 (9%)
Dose 3	NA	3 (14%)	15 (44%)	18 (32%)
Dose 4*	1 (50%)	5 (23%)	NA	5 (9%)
Dose 5	NA	1 (5%)	6 (18%)	7 (13%)
Dose 6*	NA	2 (9%)	NA	2 (4%)
Dose 7	NA	1 (5%)	2 (6%)	3 (5%)
Dose 8*	NA	3 (14%)	1 (3%)	4 (7%)
Dose 9	NA	NA	4 (12%)	4 (7%)
Dose 10*	NA	2 (9%)	NA	2 (4%)
Dose 11	NA	NA	1 (3%)	1 (2%)

NA = not applicable
[1]Note: Sponsor defined an infusion AE as an event or cluster of events that occurred during or within 2 hours after an infusion.
*Subjects randomized to the pegloticase 8 mg every 4 weeks were administered placebo infusions at Doses 2, 4, 6, 8, and 10 in order to maintain study blind.
Adapted Sponsor's Tables 37 and 40; p. 79 and 81 of ISS.

Further characterization of the most common component signs and symptoms (i.e., AEs that occurred during or within 2 hours after the end of the study medication infusion) of infusion reactions are shown in Table 31. During the controlled studies, the most commonly reported signs and symptoms associated with study infusions by patients in the every 2 week group were urticaria (11%), dyspnea (7%), erythema (6%), and flushing (6%), whereas in the every 4 week group patients reported symptoms of chest discomfort (10%), chest pain (10%), erythema (10%) and pruritus (10%). In the placebo group infusion reactions were characterized by dyspnea (2%) and flushing (2%). These rates of events for both pegloticase treatment groups remain comparable with prolonged exposure in the OLE Study 407 and on review of the data in the 120-day safety update. Overall, a higher proportion of patients in the every 2 week group (11%) reported having urticaria associated with their infusions as compared to the every 4 week group (7%) but the proportions of the other component events that could also be classified as hypersensitivity type reactions (i.e., rash, throat tightness, and wheezing) were similar for the 2 pegloticase treatment groups. The rates of these events also did not increase with increasing exposure in the OLE study or on review of the data in the 120-day safety update.

Table 31 – Tabular Summary of the Most Common Signs and Symptoms Associated with Infusion Reactions Reported by 4 or More Subjects in the Pooled Controlled Studies 405 and 406 and the OLE Study 407

MedDRA Preferred Term for Component AEs of Infusion-Related Reaction	6-Month Pooled Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Back Pain	0 (0%)	1 (1%)	6 (7%)	3 (4%)	6 (7%)
Chest Discomfort	0 (0%)	3 (4%)	8 (10%)	5 (6%)	11 (13%)
Chest Pain	0 (0%)	1 (1%)	8 (10%)	2 (2%)	9 (11%)
Chills	0 (0%)	4 (5%)	0 (0%)	5 (6%)	0 (0%)
Dizziness	0 (0%)	3 (4%)	1 (1%)	4 (5%)	1 (1%)
Dyspnea	1 (2%)	6 (7%)	6 (7%)	7 (8%)	8 (10%)
Erythema	0 (0%)	5 (6%)	8 (10%)	5 (6%)	10 (12%)
Flushing	1 (2%)	5 (6%)	7 (8%)	8 (9%)	8 (10%)
Headache	0 (0%)	1 (1%)	4 (5%)	1 (1%)	5 (6%)
Hyperhidrosis	0 (0%)	4 (5%)	2 (2%)	6 (7%)	5 (6%)
Hypertension	0 (0%)	4 (5%)	1 (1%)	4 (5%)	2 (2%)
Hypotension	0 (0%)	3 (4%)	1 (1%)	3 (4%)	1 (1%)
Muscle Spasms	0 (0%)	2 (2%)	2 (2%)	4 (5%)	3 (4%)
Nausea	0 (0%)	2 (2%)	6 (7%)	0 (0%)	6 (7%)
Pain	0 (0%)	1 (1%)	6 (7%)	0 (0%)	6 (7%)
Pruritus	0 (0%)	3 (4%)	8 (10%)	3 (4%)	8 (10%)
Rash	0 (0%)	3 (4%)	6 (7%)	3 (4%)	6 (7%)
Tachycardia	0 (0%)	3 (4%)	3 (4%)	3 (4%)	3 (4%)
Throat Tightness	0 (0%)	1 (1%)	2 (2%)	1 (1%)	4 (2%)
Urticaria	0 (0%)	9 (11%)	6 (7%)	9 (11%)	7 (8%)
Vomiting	0 (0%)	1 (1%)	3 (4%)	2 (2%)	5 (6%)
Wheezing	0 (0%)	2 (2%)	2 (2%)	2 (2%)	2 (2%)

Adapted Sponsor's Tables 44 and 93; p. 86 and181 of ISS

Immunogenicity

To assess the formation of antibodies to pegloticase, blood samples were tested that were drawn at Weeks 1, 2, 5, 9, 13, 17, 21, and 25. As shown in Table 32, approximately 88% of patients in the pegloticase every 2 weeks, 89% of patients in the pegloticase every 4 weeks treatment groups and 20 % of placebo patients tested positive for anti-pegloticase antibodies on at least one time point over the course of the controlled studies. A dose-dependent relationship with antibody titer was not apparent.

Table 32 – Tabular Summary of Number (%) of Subjects Positive for Antipegloticase Antibody for Controlled Studies 405 and 406

Anti-Pegloticase Antibody Level	Pegloticase q 2 wks (N=83) n (%)	Pegloticase q 4 wks (N=81) n (%)	Placebo (N=43) n (%)
None	10 (12%)	9 (11%)	32 (80%)
Low	24 (29%)	24 (30%)	5 (13%)
Moderate	19 (23%)	21 (26%)	3 (8%)
High	30 (36%)	27 (33%)	0
Total Number of Subjects with Anti-Pegloticase Antibodies	73/83 (88%)	72/81 (89%)	8/40 (20%)

Adapted Sponsor's Table 10.13, Appendix 10.1 of ISS

Since the presence of antibodies could potentially reduce the biological effects of pegloticase, PUA treatment responses were examined in patients subdivided by highest antipegloticase antibody titer during the combined Months 3 and 6 (Table 33). These data demonstrate that response rates decreased with increasing anti-pegloticase titer.

Table 33 – Tabular Summary of PUA Treatment Responses by Highest Anti-Pegloticase Antibody Titer During Months 3 and 6 for Combined Studies 405 and 406 (ITT Population)

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Responders: PUA < 6 mg/dL for at least 80% of the time in Months 3 and 6 Combined			
Anti-Pegloticase Antibody Level	n/N (%)	n/N (%)	n/N (%)
None	7/9 (78%)	6/7 (86%)	0/34 (0%)
Low	19/25 (76%)	13/24 (54%)	0/4 (0%)
Moderate	10/16 (63%)	9/17 (53%)	0/3 (0%)
High	0/25 (0%)	1/27 (4%)	0/0 (0%)
Total Number of Subjects Anti-Pegloticase Antibody Positive	29/75 (39%)	23/75(31%)	0/41 (0%)

Note: "n" represents the number of subjects that were PUA responders in each anti-pegloticase antibody titer category. "N" within the cells represents the total number o subjects in each anti-pegloticase antibody titer category.
Adapted Sponsor's Table A10.13, Appendix 10.1, ISS.

Antibody status can also adversely affect the safety profile of pegloticase with regard to the development of infusion reactions. Table 34 summarizes the frequency of infusion reactions observed during the controlled Studies 405 and 406. These data demonstrate that the rates of infusion reactions increased directly with increasing anti-pegloticase titers.

Table 34 – Rates of Infusion Reactions by Anti-Pegloticase Antibody Titer for the Combined Controlled Studies 405 and 406

	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Placebo (N=43)
Incidence of Infusion Reactions /Number of Subjects in Antibody Category (%)			
None	1/10 (10%)	1/19 (11%)	2/32 (6%)
Low	1/25 (4%)	4/24 (17%)	0/5 (0%)
Moderate	3/19 (16%)	9/21 (43%)	0/3 (0%)
High	16/30 (53%)	18/28 (64%)	0/0 (0%)

Adapted Sponsor's Table 11.6, Appendix 23.2, ISS.

Adverse Events Leading to Withdrawal

Patients treated with pegloticase were more likely to withdraw early due to adverse events. Table 35 below is a tabular summary of the AEs experienced by the patients who discontinued study treatment during the controlled Studies 405 and 406 and open-label extension 407. The overall proportions of patients who discontinued due to treatment-emergent adverse events were similar for the pegloticase every 2 weeks (19%) and pegloticase every 4 weeks (20%) treatment groups but were higher as compared to the placebo group (2%). Review of these data indicated that the differences in rates of premature study withdraws were primarily due to higher drop-out rates associated with infusion reactions (9% and 13%) and gout flares (6% and 4%) in the pegloticase every 2 weeks and every 4 weeks treatment groups, respectively, as compared to the placebo group (0% infusion reactions, and 1% gout flares). The rates of early subject withdrawal increased with prolonged exposure to pegloticase particularly in the every 4 week group (25%) as compared to the every 2 week group (21%). Rates of premature study withdrawal were similar in the 120-day safety update except that one patient (Subject 406-308-002) who continued to receive pegloticase every 2 weeks dropped out of the ongoing open-label extension study due to bronchitis and cardiac failure.

Table 35 – Number (%) of Subject with Who Prematurely Withdrew Due to Treatment-Emergent Adverse Events Including Infusion Reactions and Gout Flares for the Pooled Controlled Studies 405 and 406 and OLE Study 407

MedDRA System Organ Class Preferred Term	6-Month Pooled Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number of AEs Leading to Withdrawal	**3**	**16**	**33**	**20**	**39**
Number (%) of Subjects with AEs Leading to Withdrawal	**1 (2%)**	**16 (19%)**	**17 (20%)**	**18 (21%)**	**21 (25%)**
Gen. Disord. and Adm. Site Cond.:	**0 (0%)**	**8 (9%)**	**11 (13%)**	**7 (8%)**	**13 (16%)**
Infusion Reactions	0 (0%)	8 (9%)	11 (13%)	7 (8%)	13 (16%)
Fatigue	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Musculoskel. and Connect. Tiss. Dis.:	**1 (2%)**	**5 (6%)**	**5 (4%)**	**5 (6%)**	**5 (6%)**
Gout	1 (2%)	5 (6%)	3 (4%)	5 (6%)	3 (4%)
Fistula	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Gouty Arthritis	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Pain in Extremity	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Shoulder Pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Cardiac Disorders:	**0 (0%)**	**1 (1%)**	**1 (1%)**	**1 (1%)**	**1 (1%)**
Cardiac Arrest	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Extrasystoles	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Infections and Infestations:	**1 (2%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**
Localized Infection	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staphylococcal Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Investigations:	**0 (0%)**	**0 (0%)**	**2 (2%)**	**0 (0%)**	**2 (2%)**
Blood Creatinine Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Blood Glucose Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Blood Urea Increased	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Renal Creatinine Clearance Dec.	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Ear and Labyrinth Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**
Vertigo	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Gastrointestinal Disorders:	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**	**1 (1%)**
Erosive Gastritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Nervous System Disorders:	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**
Migraine	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Psychiatric Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (1%)**	**1 (1%)**
Depression	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Suicidal Behaviour	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Respiratory System Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**1 (1%)**	**1 (1%)**
Dyspnea Exacerbated	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Lung Infiltrate	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Skin and Subcut. Tiss. Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**2 (2%)**
Angioneurotic Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Urticaria	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Erythema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Hyperhidrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Surgical and Medical Procedures:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**
Abdominal Operation	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Note: If the same subject in a given treatment had more than one occurrence in the same preferred term event category, the subject was counted only once. Table amended to include the 2 subjects who discontinued from the study due to infusion reactions (C406-308-003 and C406-319-004) after the database soft lock.
Adapted Sponsor's Table 34; p. 72-3 and Table B8.4 from Appendix of ISS

Common Adverse Events

As was shown in the preceding table (Table 22), most patients (> 90%) experienced an adverse event during the controlled studies. Table 36 summarizes the most commonly reported adverse events reported by 5% or more patients at a frequency higher than 1% in the pegloticase treated population excluding gout flares and infusion reactions during the controlled Studies 405 and 406. The adverse events by preferred MedDRA term most commonly reported by pegloticase-treated patients were: headache (10%), nausea (9%), back pain (6%), nasopharyngitis (6%), and increased blood pressure (4%). With the exception of headache, these rates were comparable to those seen in placebo treated patients during these studies. No other patterns of adverse events were noted on further review of the data not shown.

Table 36 – Adverse Events Occurring in ≥ 5% of Subjects at Greater than 1% Frequency in Pegloticase-Treated Subjects Compared to Placebo (Excluding Gout Flares and Infusion Reactions) During the Controlled Studies 405 and 406

Adverse Event via MedDRA Preferred Term	Placebo (N=43) n (%)	Pegloticase q 2 wks (N=85) n (%)	Pegloticase q 4 wks (N=84) n (%)	Total Pegloticase (N=169) n (%)
Nausea	1 (2%)	10 (12%)	6 (7%)	16 (9%)
Headache	4 (9%)	8 (9%)	9 (11%)	17 (10%)
Back Pain	2 (5%)	3 (4%)	7 (8%)	10 (6%)
Contusion	1 (2%)	7 (8%)	0 (0%)	7 (4%)
Nasopharyngitis	1 (2%)	6 (7%)	4 (5%)	10 (6%)
Blood Pressure Increased	0 (0%)	0 (0%)	6 (7%)	6 (4%)
Dyspnea	2 (5%)	4 (5%)	5 (6%)	9 (5%)
Vomiting	1 (2%)	4 (5%)	5 (6%)	9 (5%)
Pruritis	0 (0%)	3 (4%)	5 (6%)	8 (5%)
Pyrexia	1 (2%)	2 (2%)	5 (6%)	7 (4%)
Chest Pain	1 (2%)	5 (6%)	4 (5%)	9 (5%)
Constipation	2 (5%)	5 (6%)	2 (2%)	7 (4%)

Adapted Sponsor's Table A8.1, Appendix ISS.

Safety Conclusions

The FDA review of safety database for pegloticase identified concerns in three main areas: 1) a higher rate of serious cardiovascular events, 2) the occurrence of infusion reactions and allergic reactions and 3) immunogenicity of pegloticase with an adverse impact on efficacy and safety. Deaths were seen in all study arms, including the placebo arm. However, the rate of mortality was higher in the controlled trials in the pegloticase every 2 week arm (3 cases or 4%) than in the pegloticase every 4 week arm (1%) or the placebo arm (1%). The deaths were related to infections and cardiovascular events and occurred in patients with multiple underlying risk factors for these adverse events. The higher rate of serious cardiovascular events was seen in both pegloticase treatment arms and demonstrated no relation to dose. The cardiovascular events showed no particular pattern and included arrhythmias, ischemic events and congestive heart failure. A consultation from the FDA Division of Cardiovascular and Renal Drug Products concluded that the distribution of cardiovascular deaths and cardiac SAEs was not obviously unusual in view of the fact that they occurred in patients predisposed to such events and taking into account the unequal randomization in the clinical trials.

A higher proportion of patients experienced serious adverse events in the pegloticase every 4 week (23%) and pegloticase every 2 week (24%) treatment groups as compared to placebo treated patients (12%) due to the high rate of infusion reactions seen in the pegloticase every 4 week (41%) and pegloticase every 2 week (26%) groups. A higher proportion of infusion reactions that were experienced by patients in the pegloticase every 4 week group (36%) were moderate-to severe intensity as compared to the pegloticase every 2 week group (18%). The occurrence of infusion reactions peaked with the administration of Dose 3 or 4 of pegloticase and declined thereafter. Pegloticase was shown to be highly immunogenic with 88% of patients in the pegloticase every 2 week group and 89% of patients in the pegloticase every 4 week group testing seroconverting to antibody positive status over the course of these studies. The magnitude of positive antibody titers to pegloticase was associated with a higher rate of infusion reactions and a decrease in urate-lowering effects of therapy.

Items for Discussion

1. Address whether the evidence indicates that pegloticase increases cardiovascular risk
2. Address whether further studies are needed to evaluate that risk
3. Address the clinical utility of pegloticase in the treatment of refractory chronic gout
4. Address the risk-benefit relationship for pegloticase
5. Address the appropriate patient population for pegloticase therapy
6. Address what should be monitored and the appropriate frequency for monitoring
7. Address what postmarketing studies would be appropriate if pegloticase is approved

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Appendices

Table 37 – Tabular Summary of Inclusion and Exclusion Criteria for Studies 405 and 406

Inclusion Criteria: Subjects included in the study were to have been:

1. Outpatients of either gender, age 18 or older (no upper age limit)
2. Hyperuricemic: screening serum uric acid must be $\geq$ 8 mg/dL
3. Patients with symptomatic gout (presence of at least 3 gout flares in the 18 months prior to entry, or at least one gout tophus, or gouty arthritis
4. Patients in whom conventional therapy is contraindicated or has been ineffective:
    a. History (either by medical record or patient interview) of hypersentivity or of failure to normalize serum uric acid with at least 3 months treatment with allopurinol at the maximum labeled dose (800 mg/dL in the United States), or at a medically appropriate lower dose based on dose limiting toxicity or dose-limiting co-morbidity
5. Willing and able to give informed consent and adhere to visit/protocol schedules (informed consent must be given before the first study procedure is performed, including washout)
6. Women of childbearing potential must have a negative screening serum pregnancy test and must use a medically approved form of birth control during their participation in the protocol. Such methods include oral, injectable, or implantable contraceptives; IUD s and barrier contraceptives in combination with spermicide

Exclusion Criteria: Subjects were to have been excluded if any of the following applied:

1. Unstable angina
2. Uncontrolled arrhythmia
3. Non-compensated congestive heart failure
4. Uncontrolled hypertension (above 150/95)
5. History of end stage renal disease requiring dialysis
6. Hemoglobulin < 8 g/dL (males) and < 7 g/dL (females)
7. Organ transplant recipient
8. Prior treatment with PEG-uricase, or other recombinant uricase, or any concomitant therapy with a PEG-conjugated drug
9. A gout flare at screening that is resolved for less than one week prior to first treatment with study drug (exclusive of chronic synovitis/arthritis)
10. Glucose-6-phosphate dehydrogenase (G6PD) deficiency
11. A history of anaphylactic reaction to a recombinant protein or porcine product, or hypersensitivity to PEG
12. Pregnancy or breast feeding
13. Has taken an investigational drug within 4 weeks prior to study drug administration or plans to take an investigational drug during the study
14. Known allergy to urate oxidase or PEGylated products
15. Has any other medical or psychological condition which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements, to complete the study.

Adapted from Sponsor Study Protocols 405 and 406

Table 38– Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Pegloticase 8 mg every 2 weeks					
405-203-001	61yo/M	Cardiac Arrest	Double Blind	No	Died despite medical resuscitation efforts following period of strenuous physical activity. H/O CHF, HTN, NIDDM, asthma, angina pectoris, end-stage cardiomyopathy (ejection fraction 17%) and insomnia. Concomitant meds: colchicine, furosemide, spironolactone, metoprolol, lisinopril, simvastatin, nitroglycerin, isosorbide, terbutaline, budesonide, celecoxib, glibenclamide, trazodone, rosiglitazone, and Tylenol #3.
406-315-005	69yo/M	Cardiac Arrhythmia	Double Blind	No	C/O weakness, aches, pains, and anorexia x 7 days S/P Study Dose 9. Evaluated by PMD on day prior to death without diagnosis and normal cardiac exam. Died in-route to hospital. H/O CAD, S/P CAGB, DM with neuropathy, PVD, bilateral edema, HTN, obesity, chronic renal failure, S/P renal artery stent, left carotid artery occlusion, and S/P right carotid endarterectomy. Concomitant meds: colchicine, omeprazole, clonidine, pravastatin, diltiazem, furosemide, metolazone, prednisone, citalopram, ASA, insulin, Kayexalate, and doxercalciferol.
406-301-003	89yo/M	MRSA Sepsis	Double Blind	Yes	Completed all 12 study infusions during double-blind study. Developed MRSA sepsis during course of antibiotics for a perianal decubitus ulcer he developed while sleeping in chair due to back pain in a nursing home. Pt. died after refusing additional antibiotics or invasive surgical procedures. H/O CAHD, S/P metal prosthetic aortic valve, cardiac arrhythmia, S/P pacemaker, PVD, HTN, hypothyroidism, dyslipidemia, and wheezing. Concomitant meds: furosemide, quinapril, coreg, dopamine, Zocor, warfarin, esomepraole, heparin, insulin, levothyroxine, metoprolol, simvastatin, tamsulosin, Zosyn, Mucinex and potassium.

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

Table 38 – Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Pegloticase 8 mg every 4 weeks					
407-122-004	54yo/F	ORSA Sepsis	OLE	No	Developed DVT and osteomyelitis of right first MTP culture positive for ORSA s/p amputation of digit. She became septic despite antibiotics and was transferred to MICU where she became progressively unresponsive and died S/P withdrawal of life support at family's request. H/O HTN, focal segmental glomerulonephritis, pancreatitis, chronic renal failure, hypercholesterolemia, peritonitis, S/P peritoneal dialysis, S/P hip fracture, and bilateral DVT. Concomitant meds: colchicine, metronidazole, vancomycin, metoprolol, amiodarone, sevelamer and aztreonam.
405-102-006	64yo/M	Kidney Failure S/P Dialysis Withdrawal Secondary to Congestive Heart Failure; End-Stage Cardio-myopathy	Double Blind	No	Hospitalized for acute dyspnea and pedal edema secondary to CHF one day S/P Study Dose 2 (blinded placebo infusion). During hospitalization the patient developed acute renal failure and was started on dialysis. Pt. requested that dialysis be withdrawn after 2 treatments. He was transferred to a hospice unit and subsequently died. H/O HTN, atrial fibrillation, CAD, S/P coronary stents, S/P pacemaker, chronic renal failure, and cardiomyopathy x 10 years (ejection fraction 10-15%) that was not reported to the study investigator. Concomitant meds: colchicine, clopidogel, ASA, digoxin, lansoprazole, furosemide, carvedilol, ramipril, amiodarone, potassium, metoprolol, glyceryl trinitrate, temazepam, alprazolam, propacet, oxycocet, and sildenafil.
406-325-001	63 yo/M	Cellulitis/sepsis secondary to necrotizing skin lesion	OLE	Yes	Pt. became septic following a course of systemic corticosteroids steroids for necrotizing skin lesions. Biopsy of skin lesions and cultures were positive for streptococcus and staphylococcus. While hospitalized he arrested and died 3 days later S/P withdrawal of life support and pressor therapy at family's request. H/O CHF, dilated cardiomyopathy, and S/P implanted cardiac defibrillator. Meds: captopril, ASA, furosemide, digoxin, metalazone, spironolactone and metoprolol. simvastatin, omeprazole, prednisone, and naproxen.

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

Table 38 – Tabular Summary of Subjects Who Died While Participating in Pegloticase Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Onset	Died >30 Days After Last Dose	Pertinent History
Placebo					
406-301-014	85yo/F	Multi-organ Failure	S/P randomization	N/A	Pt. hospitalized for unknown reasons prior to receiving first study dose during which she developed multiorgan failure and died. H/O HTN, Azotemia and Bilateral Breast CA. Concomitant meds: enalapril, metoprolol, digoxin, ASA, simvastatin, warfarin, colchine, prednisone, furosemide, valsartan, verapamil, metolazone, meclozine, and potassium.
405-101-005	67yo/M	Cardiac Disease	Double-Blind	Yes	Pt. lost to follow up S/P transfer to a rehab center post-hospitalization for a severe gout flare and urosepsis. He died 4 months after last dose of study meds. H/O CAHD, CHF, S/P cardiac stent, HTN, GERD, DM, hyperlipidemia, dsyphonia, and post-herpetic neuralgia. Concomitant meds: prednisone, pantoprazole, HCTZ, simvastatin, metoprolol, nifedpine, gabapentin, furosemide, clopidogrel, ASA, fluticasone, insulin, enalapril, Augmentin, amoxicillin, APAP, Tylenol #3.
406-311-002	80yo/M	Chronic Lymphocytic Leukemia (CLL)	Double-Blind	Yes	Pt. had stable CLL when he enrolled in study which reoccurred during Month 4 at which time he withdrew from the study and died 4 months later as a result of CLL

H/O = History of; C/O = complained of; CHF = congestive heart failure; HTN = hypertension; NIDDM = non-insulin dependent diabetes mellitus; S/P = status post; CAD = coronary artery disease; CAGB = coronary artery grafted bypass; DM = diabetes mellitus; PVD = peripheral vascular disease; CA = cancer; GERD = gastroesophageal reflux disease

Table 39 - Number (%) of Subjects with Serious Adverse Events (SAEs) Including Infusion Reactions and Gout Flares in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407

Adverse Event Via MedDRA System Organ Class (SOC) and Preferred Term	6-Month Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Number of SAE	**14**	**34**	**30**	**45**	**50**
Number (%) of Subjects with SAE	**5 (12%)**	**20 (24%)**	**19 (23%)**	**24 (28%)**	**27 (32%)**
Gen. Disorders and Adm. Site Condit.:	**0 (0%)**	**7 (8%)**	**7 (8%)**	**10 (12%)**	**10 (12%)**
Infusion Related Reaction	0 (0%)	4 (5%)	7 (8%)	5 (6%)	8 (10%)
Chest Pain	0 (0%)	1 (1%)	0 (0%)	2 (2%)	1 (1%)
Peripheral Edema	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pyrexia	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Adverse Drug Reaction	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Asthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Infections and Infestations:	**4 (9%)**	**3 (4%)**	**5 (6%)**	**3 (4%)**	**7 (8%)**
Pneumonia	1 (2%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Cellulitis	0 (0%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Bacterial Arthritis	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Staphylococcal Cellulitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Herpes Zoster	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Localised Infection	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Necrotising Fasciitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Perianal Abscess	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pyelonephritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Staphylococcal Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Infection	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Osteomyelitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Musculoskel. and Connective Tissue Disease:	**2 (5%)**	**7 (8%)**	**2 (2%)**	**9 (11%)**	**3 (4%)**
Gout	2 (5%)	4 (5%)	1 (1%)	5 (6%)	1 (1%)
Fistula	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Hemarthrosis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Steroid Myopathy	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Osteoarthritis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Synovial Cyst	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Pain in Extremity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Rotator Cuff	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Cardiac Disorders:	**0 (0%)**	**4 (5%)**	**3 (4%)**	**4 (5%)**	**3 (4%)**
Arrhythmia	0 (0%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Angina Pectoris	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Cardiac Arrest	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Congestive Cardiac Failure	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Tachycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

Note: If the same subject in a given treatment had more than one occurrence n the same preferred term event category, the subject was counted only once.
Adapted Sponsor's Tables 34; p. 72-3 and Table B8.3 in Appendix of ISS.

Table 39 - Number (%) of Subjects with Serious Adverse Events (SAEs) Including Infusion Reactions and Gout Flares in the Safety Database for the Controlled Studies 405 and 406 and Open-Label Extension Study 407 (conti.)

Adverse Event Via MedDRA System Organ Class (SOC) and Preferred Term	6-Month Controlled Studies 405 and 406			24 Month Open-Label Extension Study 407	
	Placebo (N=43)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)	Pegloticase q 2 wks (N=85)	Pegloticase q 4 wks (N=84)
Gastrointestinal Disorders:	**2 (5%)**	**3 (4%)**	**1 (1%)**	**3 (4%)**	**1 (1%)**
Gastroesophageal Reflux Disease	0 (0%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Pancreatitis	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Barrett's Esophagitis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Gastritis Erosive	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Inguinal Hernia, Obstructive	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Peritonitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Renal and Urinary Disorders:	**2 (5%)**	**0 (0%)**	**2 (2%)**	**0 (0%)**	**3 (4%)**
Acute Renal Failure	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Hematuria	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Nephrolithiasis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Metabolism and Nutrition Disorders:	**1 (2%)**	**1 (1%)**	**1 (1%)**	**3 (4%)**	**1 (1%)**
Hyperkalemia	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Hypoglycemia	1 (2%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Gout	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Nervous System Disorders:	**1 (2%)**	**0 (0%)**	**2 (2%)**	**1 (1%)**	**4 (5%)**
Convulsion	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Syncopy	1 (2%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Transient Ischemic Attack	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Carotid Artery Stenosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Injury, Poisoning and Procedural Complications:	**0 (0%)**	**1 (2%)**	**0 (0%)**	**2 (2%)**	**1 (1%)**
Facial Bones Fracture	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Injury	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Muscle Rupture	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Hip Fracture	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Neoplasms Benign, Malignant, and Unspecified (including Cysts/Polyps):	**1 (2%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**
CLL	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Malignant Melanoma	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Respiratory System Disorders:	**0 (0%)**	**1 (1%)**	**1 (1%)**	**2 (2%)**	**1 (1%)**
Dyspnea	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Dyspnea Exacerbated	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Lung Infiltration	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Blood and Lymphatic System Disord.:	**1 (2%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**
Febrile Neutropenia	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Anemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatobiliary Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**
Cholecystitis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Skin and Subcutaneous Tissue Disord.:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**1 (1%)**
Angioneurotic Edema	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Urticaria	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Vascular Disorders:	**0 (0%)**	**0 (0%)**	**1 (1%)**	**0 (0%)**	**3 (4%)**
Deep Vein Thrombosis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	2 (2%)
Hypertension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)

Adapted Sponsor's Tables 34; p. 72-3 and Table B8.3 in Appendix of ISS.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 21, 2009

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Diana L. Walker, PhD
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

Subject: DCRP consult to evaluate an imbalance in the occurrence of serious adverse events in the two confirmatory clinical trials submitted to support BLA 125293

This memo responds to your consult to us requesting we 1) assess the significance of a greater proportion of subjects in the active treatment arms experiencing cardiovascular deaths and other cardiovascular serious adverse events (SAEs) in the two pivotal trials of a novel biologic for the treatment of gout and 2) recommend if additional information is needed to define the cardiovascular safety of product administration. DCRP received and reviewed the following materials:

- Your consult dated 19 Dec 2008
- Portions of BLA 125293 including the proposed label, section 2.4 Nonclinical Overview, section 2.5 Clinical Overview, section 2.7.4 Summary of Clinical Safety, section 5.3.5.3 Integrated Summary of Safety, and clinical study reports for studies 402, 403, 405, 406 and 407 (including individual narratives for cardiovascular SAEs). Case report forms for subjects with cardiovascular SAEs were reviewed, if included in the BLA submission.
- As agreed upon with your division, we did not review amendment 8 dated 04 Feb 2009, which contains a *post hoc* adjudication of cardiac events, so as to avoid being biased in our review of the data contained in the original NDA submission.

Background

Savient Pharmaceuticals, Inc. has submitted a BLA to obtain authorization to market pegloticase for treatment of "treatment failure gout" (TFG) defined as patients with gout who have been treated with allopurinol but fail to normalize serum uric acid and have inadequate control of signs and symptoms or patients with gout who can not tolerate allopurinol. Treatment failure gout is an orphan drug population.

Gout is a disease caused by a deposition of crystals of uric acid into the articular cartilage of joints, tendons and surrounding tissues, causing inflammation and pain. It is generally associated with hyperuricemia, due to inadequate renal excretion or overproduction of uric acid. In most animals, uric acid is metabolized by uricase to allantoin, which is readily excreted in the urine. Humans are one of a few mammalian species that have an inactive uricase gene and so uric acid is the terminal product of purine metabolism. As a result blood uric acid levels in humans are 10-fold higher than in most other mammals.

Pegloticase is a monomethoxyl polyethylene glycol modified recombinant uricase produced in *E. coli.* Exogenous administration of uricase results in uric acid eing metabolized to hydrogen peroxide and allantoin.

Reviewer's comment: A brief pub med search did not reveal any known adverse cardiovascular effects of allantoin. A brief pub med search also did not reveal any known cardiovascular effects of pegylated proteins. The sponsor claims that exposure to hydrogen peroxide is minimal because the amount produced is far less than the scavenging capacity of the blood.

Nonclinical

No safety pharmacology studies were performed and no specific nonclinical evaluation of the effect of pegloticase administration on vital signs has been performed. A single long term chronic GLP toxicology study of IV administration (Covance study #7533-100) was performed in dogs. Heart rates and ECGs were recorded once prior to dose initiation and during Weeks 12, 24, 39, and 51 (recovery) at approximately 5 to 15 minutes post-dose. Blood pressure was not evaluated. There was a dose related trend toward higher heart rates in male animals but not in female animals. The significance of the findings is unclear; the metabolic milieu in the dog differs from humans because dogs are not uricase deficient.

Clinical Pharmacology

The volume of distribution of peglioticase is about 5L (i.e., about blood volume) with relatively small intersubject variability after intravenous administration. Elimination is linear with a long half-life of > 200 hours. Exposure (measured by AUC) increases approximately 50% if administered every two weeks but increases minimally if administered every 4 weeks. Doses ≥ 2 mg decrease plasma uric acid levels.

Clinical

The sponsor conducted six clinical studies of peglioticase administration to patients with gout and hyperuricemia. No studies in healthy subjects were conducted.

Phase 1 Studies:

- **Study C0401** was an open-label single ascending dose study of SC administration of 4.0 to 24 mg to 13 subjects with gout. Local site reactions, immune reactions and large intersubject variability in exposure (presumably due to differences in absorption) led to discontinuation of the study.
- **Study C0402** was an open-label single ascending dose study of IV administration of 0.5 to 12 mg over one hour to 24 subjects with gout. No SAEs or AES assessed as severe in intensity by the investigator were observed. Vital signs were collected frequently in the first week after administration. EKGs were not acquired. No significant changes in vital signs are reported.

Phase 2 Study:

- **Study C0403** was an open-label dose ranging study in which 41 subjects with "gout refractory to conventional therapy" were randomized to administration of 1) 4 mg q2 wk, 2) 8 mg q2 wk, 3) 8 mg q4 wk, or 4) 12 mg q4 wk for three months. Vital signs were collected during and between scheduled visits for administration. EKGs were acquired at screening and several weeks after the final administration. No significant changes in vital signs are reported.

Phase 3 Studies:

- **Studies C0405 and C0406** were replicate randomized, double-blind, placebo-controlled parallel group studies in which 212 subjects were randomized 2:2:1 to administration of pegloticase 8 mg IV every two weeks: pegloticase 8 mg IV every four weeks: placebo for six months. Subjects with "unstable angina," "noncompensated congestive heart failure," "uncontrolled arrhythmias," and "uncontrolled hypertension" were not eligible. Vital signs were measured prior to each infusion and periodically during infusion. 12-lead EKGs were obtained at baseline and at the end of 6 months.

- Results

  109 subjects were enrolled and 104 administered study drug in the USA and Canada in C0405. 116 subjects were enrolled and 108 administered study drug in the USA and Mexico in C0406. About 11% of the subjects reported a history of coronary artery disease, 36% cardiac disease, 17% renal failure, 13% diabetes, and 71% hypertension. Adverse events, (primarily infusion reactions and gouty attacks) resulted in discontinuation far more frequently in pegloticase treated subjects (~19%) than placebo subjects (~2%). About one third of subjects administered pegloticase had infusion reactions reported.

Reviewer's comment: It is likely that substantial numbers of pegloticase subjects were unblinded by the infusion reactions.

Systolic and diastolic blood pressure was measured at baseline, week 13, week 25, and end of study and is summarized in the sponsor's report as means with standard deviations, medians, and ranges. No pattern is discernible. 13 subjects randomized to pegloticase had AEs of "blood pressure increased" or "hypertension" whereas 3 placebo subjects did.

Reviewer's comment: Given the scanty non-systematic measurement of blood pressure, it

is not surprising that the sponsor's data are not informative. An outlier analysis might be informative.

EKGs were obtained routinely only at baseline and at end of study in trials C0405 and C0406. The sponsor reports that that 18.0 % of the EKGs of the subjects administered pegloticase 8 mg IV every two weeks became abnormal, 14.8 % of the EKGs of the subjects administered pegloticase 8 mg IV every four weeks became abnormal, and 10.5% of placebo subjects.

Reviewer's comment: The ECGs were read at the investigator's site and I could not find any attempt to control the quality of acquisition or interpretation. The sponsor should characterize the nature of abnormalities detected.

- **Study C0407** is an ongoing open-label extension study in which 149 of the 157 subjects who completed studies C0405 and C0406 are administered pegloticase 8 mg IV every two or four weeks (depending on investigator preference) for up to 24 months. The dose frequency can be changed after 6 months. 12-lead EKGs are not being acquired routinely.

No DSMB or clinical adjudication committee was used in any trial. No definition for any cardiac adverse is specified in the protocol for any study.

Cardiovascular Serious Adverse Events in all Studies

The sponsor narratives of SAEs in each clinical study report were scanned for SAEs possibly cardiovascular in nature. The CRFs of subjects who appeared to have cardiac SAEs were also reviewed if contained in the BLA submission, but most were not.

The following subjects had SAEs probably due to ischemic cardiovascular vascular disease:

1. 203-001 in trial C0405 was a 61 year-old male with ischemic cardiomyopathy and left ventricular ejection fraction of 17% taking a beta blocker, ACE inhibitor, furosemide and spironolactone. He was randomized to 8 mg pelioticase q 2 weeks and received his first dose on 28 Mar 2007. He missed doses 6 and 8. Dose 8 appears to have been held for asymptomatic hypotension; ACE inhibitor and spironolactone were discontinued. His last dose was 20 Jun at which his BP was 140/80 and bibasilar rales and pitting edema were noted. On (b) (6) he died suddenly after physical exertion.
2. Subject 122-003 in trial C0405 was 73 year-old male with a long history of cardiac disease. He was randomized to 8 mg pegloticase q 4 weeks and received his first dose and only dose of pegloticase on 03 Aug 2007. On (b) (6) he had an inferolateral MI treated by primary PCI. The subject continued in the study.
3. Subject 315-005 in trial C0406 was a 61 year old male with a long history of cardiac disease. He was randomized to 8 mg pegloticase q 2 weeks. He received his first dose of pegloticase on 29 Nov 2006 and had 8 subsequent doses with the last on 27 Mar 2007. He complained of not feeling well on (b) (6). On (b) (6) he died while being driven to the hospital.
4. Subject 101-005 in trial C0405 was a 67 year-old male with hypertension, diabetes

mellitus, dyslipidemia and coronary artery disease (CAD). He was randomized to placebo and received his first dose on 10 Oct 2006. On (b) (6) he was hospitalized for evaluation of syncope and retrosternal chest pain. He is reported to have had a small "troponin leak;" no other details are provided. Transthoracic echocardiography was consistent with an old inferior MI. The subject continued in the study.

5. Subject 301-012 in trial C0406 was a 78 year old female randomized to 8 mg pegloticase q 4 weeks. She received her first dose and only dose of pegloticase on 26 Oct 2006. She withdrew from the study on 09 Nov. (b) (6) days after withdrawing from the study she had a transient ischemic attack and recovered apparently without neurologic sequelae.
6. Subject 002003 in trial C0403 was a 77 year old female with hypertension, diabetes, and coronary artery disease administered 12 mg pegloticase q 4 weeks beginning 17 May 2006. (b) (6) days after the second infusion she had a CVA. Head CT revealed evidence of small vessel disease. Her final diagnosis was lacunar stroke. She continued in the study and received her third and final dose of pegloticase.

The following subject had a noncardiac SAE that resulted in myocardial injury:

7. Subject 110-001 in trial C0405 was 46 year-old male with a history of coronary artery disease randomized to 8 mg pegloticase q 2 weeks. He was administered his first dose on 14 Jun 2006. On (b) (6) he was hospitalized with hematemesis complicated by hypotension requiring fluid resuscitation. His initial serum troponin was minimally elevated but subsequently declined to the normal range. The investigator withdrew the subject from the study.

The following subjects had SAEs due to heart failure.

8. Subject 102-006 in trial C0406 was a 64 year old male with ischemic cardiomyopathy and left ventricular ejection fraction of 10-15%. He was randomized to 8 mg pegloticase q 2 weeks. He received his first dose of pegloticase on 13 Oct 2006 and had 1 subsequent dose on 27 Oct 2006. On (b) (6) he was hospitalized for acute heart failure. He subsequently developed acute renal failure and died in hospice a few weeks later.
9. Subject 311-005 in trial C0406 was a 67 year old male with a "cardiovascular history" s/p implantable defibrillator insertion. He was randomized to 8 mg pegloticase q 2 weeks. He received his first dose of pegloticase on 16 Jan 2007 and had 3 subsequent doses, the last on 28 Feb 2007. On (b) (6) he was hospitalized and diuresed for acute heart failure. He continued in the study.

The following subjects had SAEs due to cardiac arrhythmias.

10. Subject 301-006 in trial C0406 was a 62 year old female without previous cardiac history. She was randomized to 8 mg pegloticase q 4 weeks receiving her first dose of pegloticase on 31 Aug 2006 and her last dose on 16 Oct. She developed a supraventicular tachycardia on (b) (6), which was treated with adenosine and atenolol. She continued in the study.
11. Subject 311-005 (same subject who had CHF) in trial C0406 was a 67 year old male with a "cardiovascular history" s/p implantable defibrillator insertion. He was randomized to 8 mg pegloticase q 2 weeks. On (b) (6) he had a defibrillator shock

and then lost consciousness. Interrogation of the ICD revealed he had had an episode of ventricular tachycardia. He continued in the study.

The following subjects had SAEs most likely not cardiac.

1. Subject 124-001 in trial C0405. She was admitted for dyspnea and the event was reported as heart failure. Transthoracic echocardiogram revealed normal left ventricular function and diuresis resulted in prerenal azotemia. She continued in the study.
2. Subject 109-005 in trial C0405 was an 84 year-old male with hypertension and dyslipidemia. He was admitted for dyspnea. Transthoracic echocardiogram and adenosine perfusion imaging were unremarkable. He continued in the study.
3. Subject 311-001 in trial C0406. He was admitted for cardiac catheterization after episodes of chest pain and the event was reported as angina. He had a history of coronary artery disease. Cardiac angiography was unchanged from previous. He continued in the study.
4. Subject 301-002 in trial C0406. He was admitted for evaluation of chest pain and the event was reported as atypical chest pain. Serial cardiac enzymes were normal as was an exercise test. He continued in the study.
5. The same subject (301-002) was hospitalized for syncope. He had taken an extra dose of hie prescribed oral hypoglycemic and was found to be hypoglycemic and responded to intravenous glucose. He continued in the study.
6. Subject 327-002 in trial C0406. He was admitted for evaluation of chest pain and the event was reported as left thoracic chest pain. Serial cardiac enzymes were normal as was an exercise echocardiogram. He continued in the study.
7. Subject 301-017 in trial C0406, who had "a significant cardiac history". She went to hospital for evaluation of self-measured high blood pressure. She was admitted for evaluation of chest discomfort. Serial troponin was normal and she was not discharged on any new cardiac medications. She continued in the study.
8. Subject 118-001 in trial C0405. He was hospitalized for evaluation of chest pain about two months after he had withdrawn from the study. He had had a normal coronary angiogram within the past three years and a history of gastroesophageal reflux. Cardiac troponin was normal and his ECG was unchanged.
9. Subject 301-012 in trial C0406 had a transient ischemic attack 35 days after withdrawing from the study.
10. Subject 130-004 in trial C0406 was a 64 year old male with ischemic cardiomyopathy and implantable cardiac defibrillator. He was hospitalized for near syncope. Troponin was normal. Interrogation of the ICD was unrevealing. He continued in the study.
11. Subject 118-001 in trial C0407, who had a normal coronary angiogram in 2005. He was hospitalized two months after withdrawing for evaluation of chest pain. He was admitted for evaluation of chest discomfort. Serial troponin was normal and his EKGs were unchanged compared to baseline and did not evolve. He was not

discharged on any new cardiac medications.

12. Subject 130-004 in trial C0407, who had ischemic cardiomyopathy and implantable cardiac defibrillator. He had an episode of presyncope while a subject of trial C0406 (see above). He was hospitalized for near syncope. Creatine kinase levels were normal. He continued in the study.
13. Subject 301-017 in trial C0407, who had an episode of chest pain while a subject of trial C0406 (see above). She was hospitalized multiple times for chest pain. Serial troponin levels were normal. She continued in the study.
14. Subject 327-002 in trial C0407, who a history of cardiovascular disease. He had an episode of chest pain while a subject of trial C0406 (see above). He was admitted for evaluation of chest pain. Serial cardiac enzymes were normal as was a subsequent exercise echocardiogram. He continued in the study.
15. Subject 009002 in trial C0403 was hospitalized for chest pain twice, 1 and 2 weeks after the final infusion of study medication. EKGs and cardiac enzymes were normal. A coronary angiogram did not disclose significant coronary artery disease.

DCRP COMMENTS:

There are a number of reasons to suspect that the data used to evaluate cardiac safety may be misleading. Cardiac adverse events were not a prespecified safety endpoint in any trial so ascertainment may not be complete. Further, treatment assignment of substantial numbers of subjects in the confirmatory trials may have unblinded by infusion reactions, potentially introducing bias into investigator reporting of adverse events. Finally, it is unclear when the sponsor supplied narratives were written. If written after treatment assignment was unmasked, they are likely to be biased. This reviewer found at least one adverse event of myocardial injury that did not appear to have been identified by the sponsor. There may be other unidentified significant cardiac AEs.

Further, the lack of systematic evaluation of blood pressure and electrocardiograms renders any evaluation of the cardiac effects of pegloticase incomplete. Important mechanisms through which drugs may increase adverse cardiac outcomes include increasing systemic blood pressure, which predisposes to cardiac ischemic events and heart failure, and prolongation of ventricular repolarization, which predisposes to ventricular arrhythmias.

It is difficult to analyze *post hoc* the observed cardiovascular events without a postulating a mechanism through which they occur. If a mechanism can be postulated based on e.g. mechanism of action, nonclinical data, or a safety signal seen in earlier trials, then a reasonable hypothesis to be explored can be constructed. In the absence of a hypothesis, it is difficult to analyze the events since multiple ways of analyzing the data are possible. If multiple analyses are conducted, then the probability that one of them will appear meaningful by chance increases with each additional hypothesis.

How then should the cardiovascular safety data observed in the clinical studies of this novel biologic drug be analyzed? There is no guidance in this area. In this reviewer's opinion, considering all cardiac serious adverse events as a single group of occurrences for purposes of evaluating safety is not informative. For example, there is no causal

mechanism common to supraventricular tachycardia and myocardial infarction so considering these SAEs as part of a single group may be misleading.

This reviewer has chosen is to explore the possible association between pegloticase administration and cardiac adverse events by counting the number of events that comprise one of three common efficacy endpoints used in studies of CV drugs. Death is always the most important endpoint and counting subjects who died due to cardiovascular causes is one approach that seems valid. Ascertainment of death is likely to be complete and the only uncertainty is determining whether death is cardiovascular. Counting all the subjects who had irreversible SAEs due to ischemic vascular disease (i.e., CV death, nonfatal MI, and nonfatal stroke) should be another useful approach but may be subject to ascertainment bias; e.g., small "enzymatic" MIs without accompanying concomitant EKG changes and "silent" MIs may be less likely to be identified. Indeed, the sponsor failed to identify the SAE suffered by subject 110-001 as having a cardiac component. Lastly, counting all subjects who died or were hospitalized for events that appeared due to ischemic heart disease or heart failure could be useful because they can share some common mechanisms; hypertension for example predisposes to both. Obviously this last grouping is more likely biased than the previous two groupings since identifying the events that comprise it is more subjective.

Since there were so few events this reviewer elected to simply count events. More sophisticated analyses such as time-to-event and exposure-response are unlikely to be informative. Also, only events that occurred during the placebo-controlled trials were counted. As noted above, the population enrolled in these trials had a significant prevalence of cardiovascular disease and risk factors for cardiovascular disease so the occurrence of severe cardiac AEs was to be expected.

DCRP SUMMARY:

- None of the cardiac adverse events identified appeared unusual, i.e., they all occurred in subjects predisposed to such events. With the exceptions of subjects 301-012 and 301-006, who had reversible events (TIA and SVT respectively), all subjects identified as having serious cardiovascular adverse events had significant histories of cardiovascular disease. The population enrolled in the confirmatory trials and extension study appears to have had high prevalence of cardiovascular disease so the occurrence of some cardiac serious adverse events is expected.
- All three deaths which appear to have been due to cardiovascular disease occurred in subjects randomized to pegloticase.
- This reviewer counted six SAEs (which include the three deaths discussed above) of CV death, nonfatal MI, or nonfatal stroke; six occurred in subjects randomized to pegloticase (four q2wks and one q4wks) and one to placebo.
- This reviewer counted eight SAEs that resulted in CV death or hospitalization that appeared due to ischemic heart disease and/or heart failure; seven occurred in subjects randomized to pegloticase (five q2wks and two q4wks) and one to placebo.
- 169 subjects were randomized to pegloticase and 43 to placebo in the controlled trials. The distribution of cardiovascular deaths and of cardiac SAEs due to ischemic vascular disease and/or heart failure are not obviously unusual, even considering the

decreased duration of exposure study drug in the pegloticase groups because more pegloticase subjects withdrew prior to study conclusion.

- However, there are too few cardiac SAEs to be able to allow detection of any pattern in their occurrence resulting in a degree of uncertainty about the cardiac safety of pegloticase. The total placebo exposure in the entire development program is less than 25 subject years. And only 169 subjects were exposed to pegloticase and none for more than six months in the controlled setting. Few subjects have been exposed for more than one year. Further, no meaningful evaluation of the effect of pegloticase on vital signs or electrocardiograms has been performed.

DCRP RECOMMENDATIONS:

We recommend you request the sponsor provide

- A summary by subject of electrocardiographic abnormalities identified on the final ECGs of subjects enrolled in studies C0405 and C0406 not identified on their entry ECGs. Any evidence of interval myocardial infarction or prolongation of ventricular repolarization should be highlighted.
- An outlier analysis of the occurrence of hypertension. We are unaware of any precedent for specifying the cut points for such an analysis. In its absence, perhaps changes of > 20 from baseline at any timepoint would be useful. Additionally, an analysis of mean change from baseline divided into quartiles by treatment group could be informative.

Thank you for requesting our input into the review of this BLA. We welcome more discussion with you now and in the future.